EFFICACY OF CLOFIBRATE WITH PHOTOTHERAPY VS PHOTOTHERAPY IN NEONATAL HYPERBILIRUBINEMIA – A RANDOMISED CONTROLLED TRIAL

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CERTIFICATE

Certified that this dissertation entitled **"EFFICACY OF CLOFIBRATE WITH PHOTOTHERAPY VS PHOTOTHERAPY IN NEONATAL HYPERBILIRUBINEMIA – A RANDOMISED CONTROLLED TRIAL"** is a bonafide work done by **G.R.JAIKUMAR,** Post graduate student of Paediatric Medicine,Govt. Kilpauk Medical College and Hospital, Chennai-10, during the academic year 2011-2013.

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DECLARATION

I declare that this dissertation entitled "Efficacy of clofibrate with phototherapy vs phototherapy in neonatal hyperbilirubinemia – a randomised controlled trial" has been conducted by me at Govt. Kilpauk Medical College and Hospital. It is submitted in part of fulfilment of the award of the degree of M.D (Paediatrics) for the April 2013 examination to be held under **The Tamilnadu Dr.M.G.R Medical University, Chennai.** This has not been submitted previously by me for the award of any degree or diploma from any other university.

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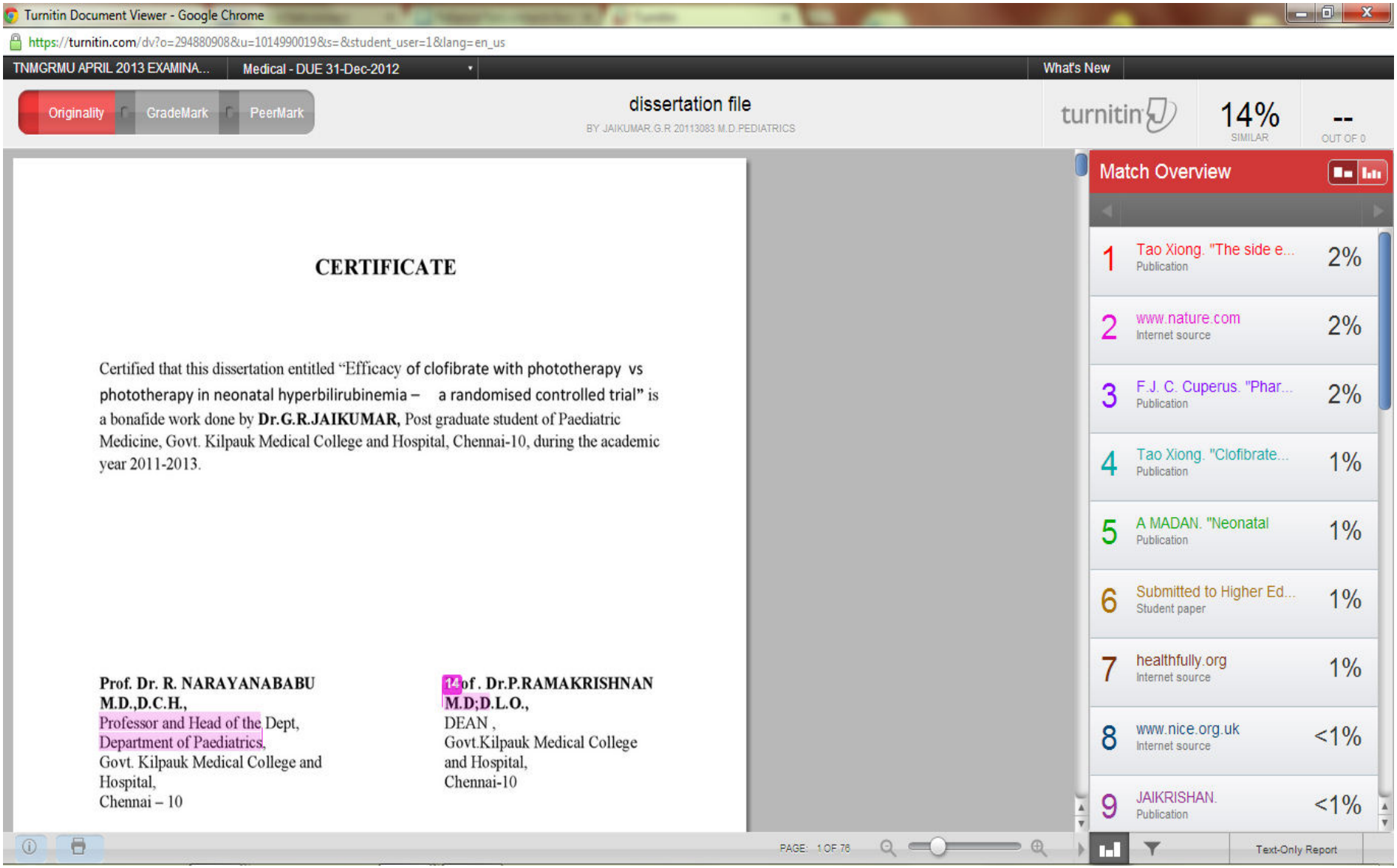
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PAGE: 1 OF 76
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CONTENTS

INTRODUCTION

Hyperbilirubinemia is yellow discolouration of sclera, skin and mucosa with elevated concentration of serum bilirubin. Neonates appear jaundiced if serum bilirubin exceeds 5 to 7 mg/dl (86-119 micro mol/l). Approximately 85% of term newborn and almost all preterm newborn develop clinical jaundice. Chemical hyperbilirubinemia is serum bilirubin greater than 2mg /dl, which is universal in all newborns. According to Maisels and Gifford[21] 97 centile bilirubin for all healthy term newborn is 12.4 mg/dl for formula fed infants and 14.8 mg/dl in breast fed newborns. Any serum bilirubin exceeding 17 mg/dl is pathologic and warrants investigation for cause.

Visual assessment of severity of serum bilirubin is done by Kramer rule . There is a cephalocaudal progression of jaundice due to maximal perfusion of face, then trunk and lastly the limbs. Apart from this the affinity of binding of albumin and bilirubin varies with distance from heart for blood in circulatory system. Jaundice in head and neck quantitates to 4 -8 mg/dl, upper trunk 5-12 mg/dl, lower trunk and thigh 8-16 mg/dl and palms and soles quantitates to greater than 15 mg/dl. This

method is not reliable as examination needs bright day light and interpretation in dark skinned individuals is difficult.

Factors making newborn prone for hyperbilirubinemiaare :

1. Increased bilirubinproduction,
2. less effective binding and transportation,
3. less efficient conjugation andexcretion and
4. Increased enterohepatic circulation.

Source of bilirubin production are RBC hemoglobin where 1 gram hemoglobin produces 34 mg bilirubin, and 25% bilirubin called Early Labelled Bilirubin produced from ineffective erythropoiesis in bone marrow and other heme containing proteins.

Neonatal hyperbilirubinemia can be of two forms: physiological jaundice and pathological jaundice. Physiological jaundice is one where visible jaundice appears after 24 hours, with peak bilirubin seen on 3to 5 days of life with bilirubin levels of 12 mg/dl. In preterm neonates peak bilirubin rising upto 15 mg/dl on day 5 to 7of life.

Pathological jaundice is one that requires evaluation and treatment. It can be characterized by onset by 24 hours of life, rise in serum bilirubin > 0.2 mg/dl/hour, sign of underlying illness, any elevation of bilirubin

Needing phototheraphy, appearance of jaundice within 24 hours of life and persistence of jaundice beyond 3 weeks and direct bilirubin greater than 2 mg/dl.

Babies with physiological hyperbilirubinemia need no treatment and careful followup to see for the progression. Pathological hyperbilirubinemia is that needs evaluation , treatment and frequent follow up. Management of neonatal jaundice includes identification of at-risk neonates, evaluating the cause of pathological hyperbilirubinemia, deciding thresholds for initiating and stopping treatment and follow-up of neonates with severe hyperbilirubinemia.

Bilirubin an antioxidant protects against freeradical injury, but still needs to treated to prevent patient developing severe hyperbilirubinemia (defined as serum bilirubin > 20 mg/dl)as it can lead to development of acute bilirubin encephalopathy. If these babies are not treated they may present chronic bilirubin encephalopathy characterized choreoathetoid cerebral palsy, complete or partial sensorineural deafness, intellectual deficits, enamel dysplasiaand limitation of upward gaze.

Treatment of neonatal jaundice is closely tied to its etiology. Early identification of risk factors and prompt close observation of these high risk neonates and initiation of timely intervention is the cornerstone of

management. Apart from initiation of phototherapy, attention should be given to ensuring adequate calorie intake and hydration status to reduce entero hepatic circulation any drug or clinical factor (sepsis, asphyxia, acidosis, temperature instability)[17,6] interfering with bilirubin metabolism, albumin binding and integrity of blood brain barrier.

Phototherapy is a modality of treatment where light of blue green spectrum with wavelength corresponding with peak absorption by bilirubin (450-460nm). Special blue lamps with wavelength of 425-475 nm are most efficient of phototherapy. When bilirubin absorbs light three types photochemical reaction namely: photoisomerisation, structuralisomerisation and photo-oxidation occur to convert bilirubin to polar form to facilitate elimination of bilirubin excretion in urine and stool. Effective phototherapy reduces serum bilirubin at the rate of 1-2 mg/dl every 4-6 hours to prevent complications of hyperbilirubinemia.

Estimation of extent and severity of jaundice can be done by estimation of transcutaneous bilirubin using transcutaneous bilirubinometer. Though this is a non invasive and easy method of measurement of bilirubin, its estimation is unreliable with serum bilirubin

above 15 mg/dl, where this the group that actually needs phototherapy and it is this group that is not identified by this device.

Followup of babies during phototherapy administration is not reliable with bilirubinometer. Transcutaneous bilirubinometer can be used as screening tool but decision to treat is to be based on serum bilirubin estimation.

Serum bilirubin comprises of two parts of conjugated and unconjugated bilirubin. Unconjugated bilirubin is the prime component that is going to increase in serum in neonatal hyperbilirubinemia due to above said reasons. Decision to treat is based on total serum bilirubin without subtracting conjugated bilirubin unless its value exceeds 50% of total serum bilirubin.

Phototherapy though effective in reducing serum bilirubin has short term[30]adverse effects like disturbance in maternal- infant interaction[01], disturbance of thermalenvironment, hypocalcemia[15], disturbance of circardian rhythm[9]and bronze baby syndrome[11] and long term side effects like retinal damage and retinopathy of prematurity[12], increasing incidence of patent ductus arteriosus, chromosomal damge[31], nevus and skin cancer.

Failure of phototherapy occurs in the setting of isoimmune or other hemolytic disease, where adjunctive therapies like intravenous immunoglobulin, phenobarbitone, tin-metalloporphyrin, oral clofibrate and oral agar have been used to reduce the progression for need of exchange transfusion.

Exchange transfusion[12] is a procedure that removes partially hemolysed and antibody coated red cells, removes unattached antibodies and replacing them with donor red cell lacking sensitizing antigen. This procedure being invasive with many short term and long term adverse effects is used as a last resort for babies with phototherapy failure and impending or early stages of acute bilirubin encephalopathy to reverse and prevent progression of brain damage.

By doing double volume exchange transfusion 87 % of patient blood volume will be replaced with fresh compatible, non hemolysed antibody and bilirubin devoid red cells. After completion of exchange transfusion there is reduction of serum bilirubin to 50 -60 % of pre exchange value and there will be a rebound of serum bilirubin to 60 % of pre exchange value in 1 hour due to rapid influx of serum bilirubin into vascular space. Further increase in serum bilirubin can occur due

continuous hemolysis of antibody coated RBC sequestered in bone marrow, spleen , senescent donor RBC and early labelled bilirubin .

Adverse events associated with exchange transfusion are

1. Hypocalcemia and hypomanesemia due binding of citrate ion to ionic calcium, which may manifest with ECG changes and cardiac dysfunction. If documented fall in serum calcium is noticed then it needs Intravenous calcium supplementation

2. Hypoglycemia is due to high content of dextrose in transfused blood causing reactive increase in endogenous insulin to cause fall in blood sugar.

3. Acid base disturbance in the form of metabolic alkalosis due to citrate in transfused blood

4. Hyperkalemia due to transfusion of stored blood, it is avoided with fresh blood transfusion and washed rbc and reconstituiting with fresh plasma.

5. Graft versus host disease due to transfusion of viable WBC which manifest with maculopapular rash, eosinopenia, lymphopenia, thrombocytopenia without other signs of immunodeficiency. This can be averted by transfusing irradiated blood

6. Thermodysregulation due of transfusion of cold blood and can be averted by adequate warming blood and use of radiant warmer.

7. Thrombovascular events in the form of thrombosis, embolism and vasospasm due to catherisation of vessels.

8. Long term events like portal vein thrombosis and can lead to extra hepatic portal vein obstruction.

Exchange transfusion is performed using push – pull technique, where sequential pulling of fixed volume of blood followed by infusing same volume of blood into the catheter. Volume of blood drawn will be 5 ml for babies < 1.5 kg, 10 ml for babies with birth weight 1.5 -2.5 kg, 15 ml for babies with birth weight of 2.5- 3.5 kg and 20 ml for babies > 3.5 kg.

These limitation of currently available treatment modalities for a preventable and reversible cause of brain damage, invokes need for newer adjunctive therapies which reduce the adverse effects of existing therapies and reduce the need of invasive therapies.

Clofibrate, the prototype of the fibric acid derivatives, is the ethyl ester of *p*-chlorophenoxyisobutyrate, which was initially introduced for treatment of dysbetalipoproteinemia and hypertriglyceridemia[21]. Its use

declined dramatically, however, after the World Health Organization reported that, despite a 9% reduction in cholesterol levels, clofibrate treatment did not reduce fatal cardiovascular events, although nonfatal infarcts were reduced. Clofibrate is now used in treatment of neonatal jaundice as it induces glucuronyl transferase[10] thereby enhancing bilirubin conjugation and better excretion in bile. This action acts as an adjunct to phototherapy holds promise to reduce the phototherapy failure rates and duration of phototherapy.

The present study is to determine whether clofibrate therapy for neonatal jaundice decreases the duration of phototherapy, incidence of phototherapy failure rates and preventing further increase in serum bilirubin without any adverse effects.

REVIEW OF LITERATURE

Bilirubin an end product of heme metabolism is derived from hemoglobin , myoglobin, cytochrome, catalase, peroxidase and free heme. Heme ring of heme containing compounds are oxidized in reticuloendothelial system by hemeoxygenase to biliverdin and release of carbon monoxide. Biliverdin is reduced to bilirubin by biliverdin reductase.

Bilirubin formed is nonpolar, insoluble in water, transported to liver bound to albumin. Albumin bound bilirubin being fat soluble dissociates from albumin and crosses the plasma membrane and binds to cytoplasmic ligandin to enter the endoplasmic reticulum. Here bilirubin is conjugated by uridinediphosphate glucuronyl transferase to diconjugate form to be excreted into the bile canaliculi. This enzyme is induced by clofibrate to enhance conjugation and excretion.

Conjugated bilirubin in gastrointestinal tract is converted to unconjugated bilirubin by intestinal glucuronidase enzyme to enter enterohepatic circulation or acted by intestinal bacteriato be converted to urobilinoids to be excreted in stool and urine as urobilin and stercobilin respectively.

Bilirubin in circulation is predominantly unconjugated and it is bound to albumin. Bilirubin bound albumin is unable to cross the blood brain barrier.1 gram of albumin binds with 8.5 mg/dl of bilirubin serum albumin level directly correlates to the gestational age and postnatal age and adult values are usually attained by 5 months of age.

There is structural differences in albumin configuration and this resolves with maturity attaining adult characteristics by10-12 months of age. Albumin is also the binding site for acidic drugs and in competition for albumin binding sites these acidic drugs displace bilirubin to enhance toxicity. Bilirubin : albumin ratio exceeding 8 in term non sick neonates, > 7.2 in term sick neonates and stable preterm neonates with gestational age above 35 weeks upto 37 completed weeks of gestational age, > 6.8 in sick preterm neonates with gestational age above 35 weeks upto 37 completed weeks of gestational age [2] increases the risk of brain damage and brain deposition of bilirubin.

Factors[7] that increase susceptibility to bilirubin induced neurological dysfunction are asphyxia, sepsis, hyperthermia, acidosis, hypoalbuminemia, acidosis, low birth weight, preterm babies, hemolysis, prolonged hyperbilirubinemia and caloric deprivation.

Factors that enhance bilirubin deposition into brain [27] are increase in free bilirubin, reduction in amount or binding capacity of albumin which increases the precipitation of bilirubin acid in nerve cell membrane. Disruption of blood brain barrier and acidosis enhance brain damage.

Bilirubin deposition occurs in basal ganglia, pons, cerebellum. Deposited bilirubin causes disruption of neurotransmission, mitochondrial dysfunction, intracellular membrane impairment and interferes with cellular enzyme activity. By these activities they cause pigmentation and necrosis of the neural tissue Kernicterus causes selective yellow staining in the basal ganglia(globus pallidus and subthalamic nucleus). Brainstem nuclei, especially the auditory (cochlear nucleus, inferior colliculus, superior olivary complex), oculomotor and vestibular nuclei are increasingly vulnerable. Other susceptible areas are the cerebellum (Purkinje cells) and the hippocampus especially the CA2 sector.

Acute bilirubin encephalopathy consists of reduced feeding, lethargy, variable abnormal tone (hypotonia and/or hypertonia), high pitched cry, retrocollis and opisthotonus, sunsetting sign, fever, seizures, and death. Laboratory evidence ranges from increased abnormal

brainstem evoked response interwave intervals I–III and I–V and decreased amplitude waves III and V to absent response[28], and MRI manifest with acute abnormalities in the globuspallidus and subthalamic nucleus.

Chronic bilirubin encephalopathy (kernicterus) is a clinical tetrad consisting of (1) a movement disorder consisting of not only of athetosis and dystonia, but also include spasticity and hypotonia, (2) auditory dysfunction consisting of hearing loss and auditory neuropathy or auditory dyssynchrony, (3) oculomotor impairments in the form of impairment of upgaze and lateral gaze impairments including strabismus, and (4) dental enamel hypoplasia of the deciduous teeth.

Phototherapy is the sheet anchor in treatment of neonatal jaundice. Bilirubin when absorbs phototherapy light three types of photochemical reaction occur. They are: 1.Photoisomerisation, 2. Structural isomerisation, 3. Photo-oxidation.Phototherapy light acts on bilirubin bound to albumin in cutaneous capillaries and interstitial space.

Photoisomerisation converts 4z 15z unconjugated bilirubin to less toxic, polar 4z 15eform which is excreted in bile. This process is reversible and results in enterohepatic circulation with rapid reabsorption from gut. Structural isomerisation is intramolecular cyclization of

bilirubin to lumirubin, which contributes 2% to6% serum bilirubin during phototherapy resulting in bile and urine excretion. Photo-oxidation is least important reaction converting bilirubin to small polar products that are excreted in urine.

Factors[17]that determine the efficacy of phototherapy spectrum of light, irradiance, surface area and duration of phototherapy. The best spectrum of light is 425 to 475 nm, the blue green spectrum. Irradiance of light depends on distant from the light source and neonate. The phototherapy lights are placed at 20 cm from baby to increase the irradiance. Surface area exposed to phototherapy is enhanced by double surface phototherapy and use of aluminium foils in margin of phototherapy unit.

Phototherapy can be administered by : 1. Compact fluorescent light tubes which are very effective in reducing bilirubin 2. Halogen lamps, though compact cannot be kept close to baby due to risk of burns and spectral power produced by these lights is lower than that produced by compact fluorescent light tubes,3. Fibreoptic systems, is very effective in delivering phototherapy and they don't have the hazard of causing retinal damage and are useful for home phototherapy, 4.Light emitting

diodes is very effective in generating adequate irradiance and spectral power to provide effective phototherapy.

Phototherapy causes fall in serum bilirubin by 1 to 2 mg/dl every 4-6 hrs of phototherapy. If serum bilirubin continues to rise despite phototherapy to reach threshold of exchange transfusion is considered failure of phototherapy. To avoid this situation adjunctive therapies have been developed . Intravenous immunoglobulin is used in isoimmune hemolytic causes wherein they act by blocking the Fc receptor to bring down hemolytic rate. Cost of the treatment is the limiting factor and useful in immune hemolysis cases only. Other modalities are phenobarbitone to cause enzyme induction of uridine diphosphateglucuronyltransferase. This treatment has long latency period with 48 to 72 hours of administration to have effect on enzyme induction and respiratory depression and lowering serum vitamin k levels as side effect. Phenobarbitone on long term administration is effective in lowering serum bilirubin in babies with crigglar najjar syndrome type II and it is one of the effective therapies of this disease.

Oral agar, charcoal used as bilirubin binding agents lower the enterohepatic circulation mediated rise in serum bilirubin. Use of oral agar causes increase in stool frequency to cause increase clearance of

intraluminal bilirubin. But the research project are in primitive stages resulting in inhibition of widespread usage of these drugs. Heme oxygenase inhibitors like metalloporphyrins inhibit production of bilirubin and thereby need of phototherapy. Potency of metalloporphyrins depend on the nature of side chain and central metal cation. Ethyl group side chain are more potent than any other side chain. However these donot bind molecular oxygen, so they are not metabolically degraded. There is unceratinity in form metalloporphyrin to be used like tin, zinc, cobalt form and data regarding side effects and tolerability are limited. These metalloporphyrins are to be administered intramuscularly and their effectiveness depends on the dosage administered.

Clofibrate used in neonatal jaundice as a enzyme inducer has shown in preliminary studies to reduce the failure rates of phototherapy and duration of phototherapy. The dose needed to achieve this is of single dose thereby obviating the problem of compliance. This drug is also in its preliminary stages regarding the correct dosage for best effect and least possible adverse effect, its use in immune hemolytic jaundice which is the prime cause of phototherapy failure. This invokes further research in this subject.

Phototherapy though the most effective way to treat neonatal jaundice is now found to have significant adverse effects these effects are of short term and long term nature. Short term effects is that it affects mother infant bonding. Phototherapy separates neonates from mothers, which might interfere with establishing parent–child bonding in the era where the concept rooming in and mothering in is promoted in baby friendly hospital initiative. Fluorescent lamps routinely used in phototherapy changes the thermal environment of infants, which leads to increased insensible water loss, hypothermia, hyperthermia, and dehydration. Phototherapy can lead to decreased total and ionized calcium levels, especially in preterm neonates. This effect is attributed to increased urinary calcium excretion . In addition, light can affect calcium homeostasis by inhibiting pineal secretion of melatonin and consequently leading to hypocalcemia. Decreased plasma levels of melatonin, alters the normal circadian rhythms and leading to abnormal behaviors such as frequent crying and jitteriness.

Phototherapy affects the Th-2/Th-1 switch, causing allergic diseases during childhood and later in life. Phototherapy can significantly increase the levels of cytokines, including TNF-alpha, IL-1 beta, and IL-8, but decrease the level of IL-6 This change of cytokine levels is considered to be the principal cause of Th-2/Th-1 switch disorder.

Phototherapy induced chromosomal and DNA breakage induces defective lymphocyte function and defective TH2/TH1 switch.

Penetration is enhanced in neonates who are being exposed to a higher spectral irradiance of phototherapy. The light photon causes the relaxation of aortic smooth muscle through the activation of the nitric oxide–cyclic GMP pathway and Ca2+-dependent K+ ion channels. This causes reopening of ductus arteriosus. Photon absorption is dramatically increased in the retina during blue light exposure, increasing the susceptibility to light-induced cell death in the retina to cause retinal damage. Bilirubin plays a role as an antioxidant, so ROP might be mitigated by bilirubin.

With the above side effects and chance of failure in certain group patients it obviates the need of new form of therapy that would be adjunctive or substitute or prevent patient from exposed to phototherapy. Of the above said adjunctive therapy clofibrate promises to effective, safe readily available modality with single dosing eliminating compliance issues.

Clofibrate the prototype of the fibric acid derivatives, is the ethyl ester of *p*-chlorophenoxyisobutyrate. In 1962, Thorp and Waring reported that ethyl chlorophenoxyisobutyrate lowered serum lipid levels in rats. In

1967, the ester form clofibrate was approved for use in the United States and became the most widely prescribed hypolipidemic drug. Its use declined dramatically after the World Health Organization reported that, clofibrate treatment did not reduce fatal cardiovascular events, although nonfatal infarcts were reduced. Fibrates reduce triglycerides through peroxisomal proliferator activation receptor alpha -mediated stimulation of fatty acid oxidation, increased lipoprotein lipase synthesis, and reduced expression of apoC-III. An increase in lipase would enhance the clearance of triglyceride-rich lipoproteins. A reduction in hepatic production of apoC-III, which serves as an inhibitor of lipolytic processing and receptor-mediated clearance, would enhance the clearance of VLDL. Fibrate-mediated increases in HDL-C are due to PPARa stimulation of apoA-I and apoA-II expression, which increases HDL levels.

Clofibrate treatment also increases the hepatic conjugation of UCB *Via* induction of glucuronyl transferase enzyme in liver. Its potency in enzyme induction is three times that of phenobarbitone. Clofibrate[10] treatment in Sprague-Dawley rats increased glucuronyltransferase activity and resulted in an 84% increase in the hepatic clearance of IV-administered unconjugated bilirubin. This drug is proposed to reduce the duration of phototherapy and failure of phototherapy.

Lindenbaum *et al.*[19,20] published the first randomized placebo-controlled trial with clofibrate in 1981, involving 93 full-term neonates with physiological jaundice. Of these 93 neonates, 47 received one oral dose of clofibrate, which significantly lowered plasma UCB levels from the 6th hour after administration and curtailed the duration of jaundice. A study in 89 preterm neonates showed comparable results, including indications for a dose-response relationship: the hypobilirubinemic effect correlated with the plasma level of clofibrate.

Zahedpasha et al did a randomized trial in healthy term newborns with birth weight above 2.5 kg and randomized 60 babies into two groups of 30 babies excluding babies with hemolytic disease of newborn. The baseline variables in term of sex distribution , mean age at start of phototherapy, and mean bilirubin at start of phototherapy were not significantly different between two groups. They concluded that clofibrate had significant reduction in duration of phototherapy and and mean bilirubin at 24 and 48 hours of treatment.

Eghbalian et al performed a randomized trial in 30 term babies in clofibrate group and 30 babies in control group. These babies were similar in baseline serum bilirubin. They found that clofibrate group patient had significant reduction in duration of phototherapy,and mean

bilirubin at 24 and 48 hours after start of phototherapy. They concluded that clofibrate is effective in treatment of neonatal jaundice in term neonates.

Fallah et al performed a randomized trial in term newborns with birth weight > 2.5 kg and there 30 babies in each group. In this study clofibrate was administered orally at a dose of 5o mg/kg at the start of phototherapy. The mean bilirubin at the start of phototherapy was similar in both group. They measured two outcomes, and found that clofibrate group had significant reduction in duration of phototherapy where the clofibrate group needed treatment for 30 hours against 46 hours in phototherapy alone group and 2 patients had episodes of loose stool of reported side effects in clofibrate group. It was found that clofibrate even at a dose of 50 mg/kg had same effect in decreasing the duration of treatment.

Habibi et al performed a randomized trial with 52 babies in total , with 26 babies in each group. They performed a randomized trial in term babies with birth weight > 2.5 kg. The baseline characteristics of mean birth weight, sex distribution, mean hours of life at start of phototherapy and mean baseline bilirubin at start of phototherapy were similar in either groups. Babies were administered 100 mg/kg clofibrate at start of

phototherapy and the outcomes measured were duration of phototherapy, peak bilirubin and adverse events occurrence. It was found serum bilirubin levels after 24 hours of start of treatment in clofibrate was lower than control group and decrease in duration of phototherapy without any adverse events.

Sharafi et al had their mean duration of phototherapy in their study to be 72 hours in clofibrate group and 76.80 hours in control group, in a study performed to study the effect of clofibrate in neonatal jaundice involving 60 babies with 30 babies in each group. The results also showed decrease in mean serum bilirubin at 24 and 48 hours after start of phototherapy. This study was performed in 60 term babies with weight above 2.5 kg and 50 mg/kg dose was administered and all the babies were at home therapy

Three randomized controlled trials[34,35], each involving 60 full-term neonates, compared the use of clofibrate and phototherapy with the use of phototherapy alone. Clofibrate, as add-on treatment to phototherapy accelerated the decrease in serum total bilirubin concentrations and it was found in all of these trials to decrease the duration of phototherapy.

Clofibrate has been tested in different situations of neonatal jaundice. In 2011morteza *et al* conducted a study to evaluate the

therapeutic effect of clofibrate in neonatal hyperbilirubinemia in 52 newborns . Drug increases liver bilirubin clearance rate to 100% within 6 hours and the study concluded that clofibrate was effective in reducing mean serum bilirubin values at 24 and 48 hours after start of phototherapy in term newborns with non hemolytic neonatal jaundice. Yadollah *et al* assessed the efficacy of clofibrate in neonatal jaundice in 40 patients with glucose 6 phosphate dehydrogenase deficiency. The mean serum bilirubin was significantly lower during phototherapy in patients with single dose of clofibrate of 100 mg/kg. They concluded that clofibrate induces a faster decline in serum total bilirubin level, a shorter duration of phototherapy and hospitalization without any side effects in full term G6PD deficient neonates with jaundice.

Zahedpasha et al did another randomized trial to study the duration of treatment, peak bilirubin, adverse events and exchange transfusion performance in term neonates with birth weight above 2.5 kg and included babies with glucose 6 phosphate dehydrogenase deficiency babies and excluding babies with blood group incompatibility and they found that clofibrate brought about significant reduction of phototherapy duration, failure of phototherapy and peak bilirubin.

Studies including hemolytic disease of newborn are very few. Since glucose 6 phosphate dehydrogenase deficiency which induces spontaneous hemolysis in severe forms of the disease and hemolysis on exposure to triggering factors and stressful situation in milder disease and this being very common in Middle East Asian region. This study was performed by Zahedpasha in Iran showed significant reduction in duration of phototherapy. Apart from this Flores –nava did trial involving 45 babies including both term and preterm babies with ABO and Rh incompatibility using 100 mg/kg clofibrate and they found significant decrease in duration of phototherapy and need of exchange transfusion. Similarly Lindenbaum studied 93 babies in study and only term babies were included including ABO and Rh incompatibility. The assessed the peak bilirubin and need for exchange transfusion and found significant reduction in both outcomes observed. This shows that there is paucity of data involving hemolytic disease of newborn and this shows need to study in large sample of babies with Rh and ABO incompatibility in our setting.

Ashraf et al conducted a randomized double blinded placebo controlled trial on efficacy of clofibrate in neonatal hyperbilirubinemia in preterm newborn babies. They had concluded that effect of clofibrate on treatment of jaundice was not significant difference in peak bilirubin

between the two groups, though duration of phototherapy has been decreased significantly in clofibrate groups.

Sakha et al performed a randomized controlled trial involving 30 babies in clofibrate group and 30 babies in phototherapy group in term and late preterm babies. The babies had comparable baseline characteristics in either group with regards to gestational age , mean bilirubin at start of phototherapy and mean age in hours of life at start of phototherapy. Here babies received 100 mg/kg of clofibrate within 12 hours of phototherapy. They measured outcomes of peak bilirubin, duration of phototherapy, rebound jaundice and adverse events following phototherapy administration. They concluded that there was significant decrease in mean serum bilirubin at 24 and 48 hours after of phototherapy and good decrease in duration of phototherapy. There was no significant rebound increase in serum bilirubin and no reported side effects.

Sedigheh et al did a randomized controlled trial involving 68 healthy late pre-term newborns with non-hemolytic jaundice and neonates that did not need urgent exchange transfusion. They analysed the bilirubin values after 48 hours of phototherapy administration and duration of phototherapy and they found that mean duration of phototherapy was 64 .32 hours in the study group in comparison with

control group with 87.84 hours with significant reduction in duration of phototherapy and mean TSB 48 hours after phototherapy was 8.6 mg/dl in clofibrate group and it was 10.94 mg /dl in phototherapy group with no significant difference in mean bilirubin at 48 hours of treatment. This study though included stable preterm newborn, did not include babies with hemolytic disease.

Caballero-noguez et al performed and randomized trial involving 12 babies in clofibrate group and 9 babies in phototherapy involving preterm newborns with gestation age above 28 weeks . They measured outcomes such as adverse effects and need of exchange transfusion and there was no reported adverse effects and no baby needed exchange transfusion. Drawback of this was they failed to measure the duration of phototherapy and peak bilirubin and the sample size was small , making the need of study with large sample size . The positive aspect of the study was that they included preterm newborns of gestation age upto 28 weeks and the study could suggest that it was safe even in preterm newborns. Thus uptodate there is no well performed study on preterm to suggest the effectiveness of this drug in preterm neonates

Clofibric acid is the main metabolite of clofibrate, which has the effective plasma concentration of 140μg/mL for jaundiced neonates. In

humans, most of the plasma clofibric acid is in bound state to albumin. Decreased level of albumin in preterm infants will lead to increased free form of clofibric acid, which will facilitate rapid clearance of clofibric acid and results in lower plasma levels of clofibric acid. This invokes the need of higher dose in preterm and sick neonates with low serum albumin. Clofibrate has been used in different dosages from 25 mg/kg single dose to 100 mg/kg single dose. There has not been significant variation in results. Moslehi[25] et al performed a randomized controlled trial to study the effect of low dose (25mg/kg) in neonatal jaundice. They randomized patients into three groups where one group received 25 mg/kg of clofibrate, another group received 50 mg/kg and last group received only phototherapy. The mean serum bilirubin was significantly lower in either clofibrate groups and mean duration of phototherapy was significantly lower in either clofibrate group. They concluded that lower doses of clofibrate can be used with the same therapeutic efficacy in reducing TSB levels in term infants and there was no side effects in either group of clofibrate treatment .

Side effects with clofibrate drug therapy have noticed in long term therapy for treatment of hyperlipidemia. The reported adverse effects have been Gastrointestinal side effects occur in up to 5% of patients. Other side effects are reported infrequently and include rash, urticaria,

hair loss, myalgias, fatigue, headache, impotence, and anemia. This has been with chronic drug intake. In treatment of neonatal jaundice single dose is used and dosage used is less than the dose for treatment of hyperlipidemia.Tao[29] et al had conducted a systematic review on 13 randomised controlled trials and 2quasi randomized controlled trials involving 867 neonates involving neonatal jaundice, where varying doses of clofibrate used showed no significant side effects in the follow up period of 2 weeks to 2months, except 1 case of cholestasis. The follow up duration was short in various studies and none of the above said side effects have been reported in the single dosing in infants.

Cochrane review[12] done by Gholitbar M et al to evaluate the efficacy of clofibrate in neonatal jaundice to determine the following outcomes :

1. Mean change in bilirubin levels (mg/dL or μmol/L) over 24 hours, 48 hours, 72 hours.
2. Mean duration of treatment with phototherapy (hours),
3. Number of exchange transfusions needed,
4. Any adverse effects of clofibrate,
5. Bilirubin encephalopathy,
6. Neonatal mortality.

This review was conducted involving Fifteen studies of which two included preterm neonates and 13 had included term neonate. All the studies were conducted in Iran except one study. They concluded that there was reduction in peak bilirubin at 48 hours and duration of phototherapy in preterm newborns. In term newborns also there was reduction in duration of phototherapy, mean bilirubin was reduced at 24 hours and 48 hours after start of phototherapy. They also analysed the data on efficacy of clofibrate at different doses and found studies in term newborns at doses of 50 mg/kg and 25 mg/kg and found that they were effective in reducing the duration of phototherapy and mean bilirubin at 24 and 48 hours of phototherapy. There was also significant reduction in need of exchange transfusion and found no significant adverse effects.

They concluded that evidence that clofibrate in combination with phototherapy has a beneficial effect on the duration of phototherapy needed for neonates with hyperbilirubinaemia and rates of exchange transfusion were quite low with only three neonates requiring an exchange transfusion in all the studies, which is to be expected with the effectiveness of phototherapy There are limitations in advocating routine use of clofibrate as an adjunct to phototherapy as there is limitation of date on long term safety profile of the drug, its efficacy is yet to be tested in sufficient cases of immune hemolytic jaundice. There are no data to

show whether the drug treatment modifies the rate of kernicterus or long-term neuro developmental impairment due to bilirubin encephalopathy or risk of death.

From the above review clofibrate is effective at lower dose and has reported no side effects and at the same stage is very effective in treatment neonatal jaundice. Data is still lagging in studies outside Iran and treatment of preterm babies and those with hemolytic disease.

This obviates the need of studies in large sample with inclusion of isoimmune jaundice with need for long term followup of subjects to study the safety of this drug. After the review of literature, justifying that immaturity of hepatic system in conjugating bilirubin plays one of the important causes of presentation of neonatal jaundice and this opens new avenues of research needed to find adjunctives to phototherapy in treatment of jaundice.

AIMS AND OBJECTIVES OF THE STUDY

To assess the efficacy of clofibrate with phototherapy versus Phototherapy in treatment of neonatal hyperbilirubinemia

Outcomes measured:

1. peak bilirubin

2. duration of phototheraphy

3. need of exchange transfusion

RESEARCH HYPOTHESIS

Adjunctive usage of clofibrate with phototherapy reduces the duration of phototherapy, reduces the occurrence of failure of phototherapy by induction of enzyme glucuronyl transferase and prevents the rise of serum bilirubin during phototherapy treatment.

MATERIALS AND METHODS

STUDY DESIGN

Double blinded randomized controlled trial

STUDY PERIOD

January 2012 to November 2012

STUDY POULATION

Intramural and extramural newborns admitted for neonatal jaundice in Neonatal Intensive Care Unit, Government Kilpauk Medical College Hospital, Chennai-10.

INCLUSION CRITERIA

Term neonates with birth weight> 2.5 kg with total serum bilirubin values meeting the threshold for phototherapy according to age specific nomogram by American Academy of Paediatrics[2] for phototherapy.

EXCLUSION CRITERIA

1. preterm
2. newborn with sepsis, asphyxia, shock
3. congenital anomalies
4. small for gestation/ intrauterine growth restriction
5. neonatal cholestasis
6. Inborn errors of metabolism
7. neonates already started on phototherapy before referral
8. neonates with renal or liver disorders
9. neonates with coagulation disturbances
10. neonates with acid base disturbance, electrolyte disturbance
11. neonates with features of intrauterine infection

GROUPS ASSIGNED

1. Clofibrate with phototherapy

2. Phototherapy

DRUGS USED

Single dose of 25 mg/kg clofibrate tablet dissolved in expressed breast milk given at the start of phototherapy per oral route

METHODOLOGY

Neonates found to be icteric on clinical examination were subjected to serum bilirubin evaluation and those babies with serum bilirubin crossing the cut off value for phototherapy by AAP nomogram for phototherapy or exchange transfusion were assessed for exclusion factors. If exclusion factors were absent they were enrolled into the after obtaining written and informed consent. These babies were randomized to either of the group using randomization table. Neonates of the clofibrate group were given single oral dose of clofibrate 25 mg/kg dissolved in expressed breast milk fed through paladai before the start of phototherapy. Neonates of the control group were given 0.5 ml of multivitamin drops dissolved in expressed breast milk fed through paladai. Babies of both the group were subjected phototherapy at a distance of 20 cm under phototherapy unit with 6 fluorescent lamps of blue light spectrum continuously with interruption of phototherapy only during breast feeding.

Babies were continuously monitored clinically and evaluated for development of side effects of either therapy in both groups. Serum bilirubin was monitored at the start of phototherapy and every 12 hours .

Phototherapy was stopped when serum bilirubin fell 2mg/dl below age specific threshold according to AAP nomogram.

Neonates whose bilirubin continued to rise despite intense phototherapy were subjected to exchange transfusion when bilirubun level crossed the threshold for exchange transfusion as per AAP nomogram.

At the start of phototherapy neonates were evaluated for their blood group, maternal blood group, coombs evaluation, peripheral smear evaluation, liver function test, renal function test and daily weight monitoring. Serum bilirubin was monitored for 12 hours after stopping phototherapy and if no rebound rise occurred ,babies were discharged 24 hours after stopping phototherapy. Babies discharged were followed up 1 week after discharge for weight gain , features of cholestasis, feeding and bowel pattern and clinical evaluation were performed.

Data regarding the sex, birth weight, hour/day of life, maternal and baby blood group, bilirubin at the start of treatment and peak bilirubin were recorded. Duration of phototherapy, failure of phototherapy, if any were recorded. Monitoring and follow up data were recorded. Babies were managed as per standard protocol and were assessed frequently for

development of any complication. Data obtained were analyzed for statistical significance.

Discrete variables were analyzed by chi-square test and continuous variables by z test. P value < 0.05 was considered as statistically significant.

RESULTS

The study was conducted in newborns admitted as neonatal hyperbilirubinemia in the Neonatal Intensive Care Unit (NICU), Department of Paediatrics, Kilpauk Medical College & Hospital, Chennai. Both intramural and extramural babies were included in this study. Study was conducted over a 11 months period, extending from January 2012 to november 2012.

During this study period 415 neonates were treated for hyperbilirubinemia with phototherapy. Of this 198 cases met the inclusion criteria and were enrolled into the study. 99 babies were randomized to clofibrate with phototherapy group and 99 babies were randomized to phototherapy alone group. Babies in the clofibrate with phototherapy were given single dose of clofibrate 25 mg/kg at start of phototherapy and were continued on phototherapy as per protocol.

Babies were monitored with serum bilirubin every 12 hours and were monitored for any complication in either group. Babies were discharged after 24 hours of stop of phototherapy and babies were followed up after 1 week. There were no babies who were lost to follow up.

Group	No .of neonates
Clofibrate with phototherapy	99
phototherapy	99

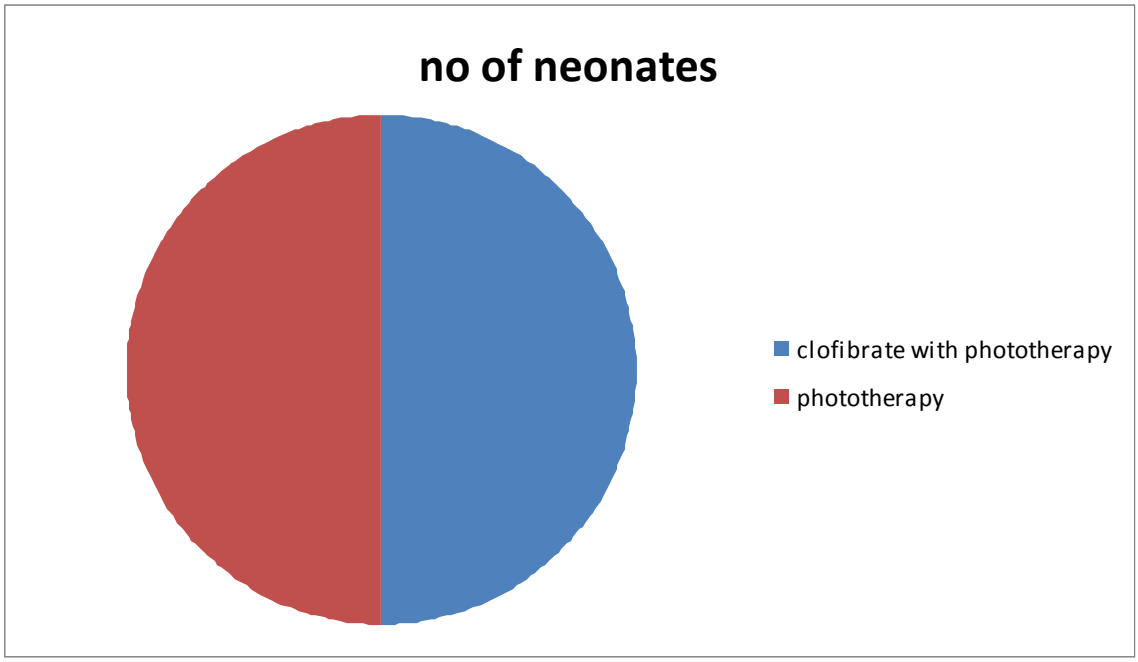


Fig 1: number of neonates in either groups

SEX DISTRIBUTION

In phototherapy group there were 54 male babies and 45 female babies. In clofibrate group there were 56 male babies and 43 female babies

Group	Male(%)	Female(%)
Clofibrate with phototherapy	56 (56.56%)	43(43.43%)
phototherapy	54(54.54%)	45(45.45%)
total	110(55.55%)	88(45.45%)

CHI SQUARE TEST

	value	Degree of freedom	P value
Chi square	0.081	1	p>0.05
No. of valid cases	198		

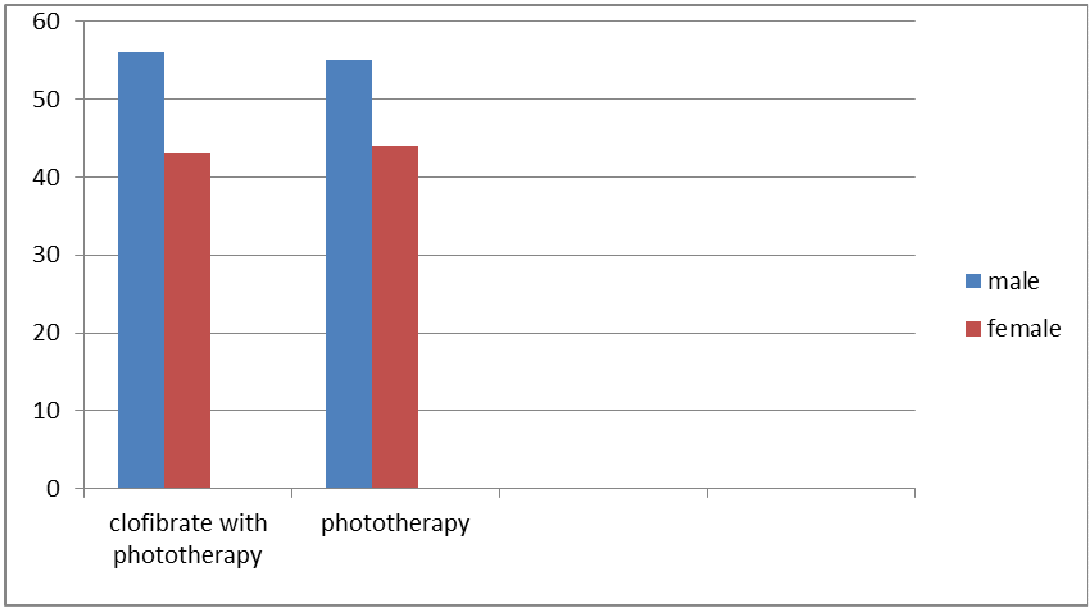


Fig2: sex distribution in either groups

Though there were more number male babies in either group but the sex distribution was statistically insignificant with p value> 0.05. The increase in number of males presenting jaundice substantiates the fact that male babies are at increased risk of jaundice.

HOURS OF LIFE AT START OF PHOTOTHERAPY

The mean hours of life in either group at start of phototherapy is depicted in table below.

group	Mean hour of life(+/- SD)
Clofibrate with phototherapy	58.91 hours(+/-18.39)
phototherapy	60.54 hours(+/-16.07)

The mean hours of life at start of phototherapy was 58.91 hours and 60.54 hours in clofibrate and phototherapy respectively.

When analysed with Z test there was no significant difference in either group with pvalue>0.05

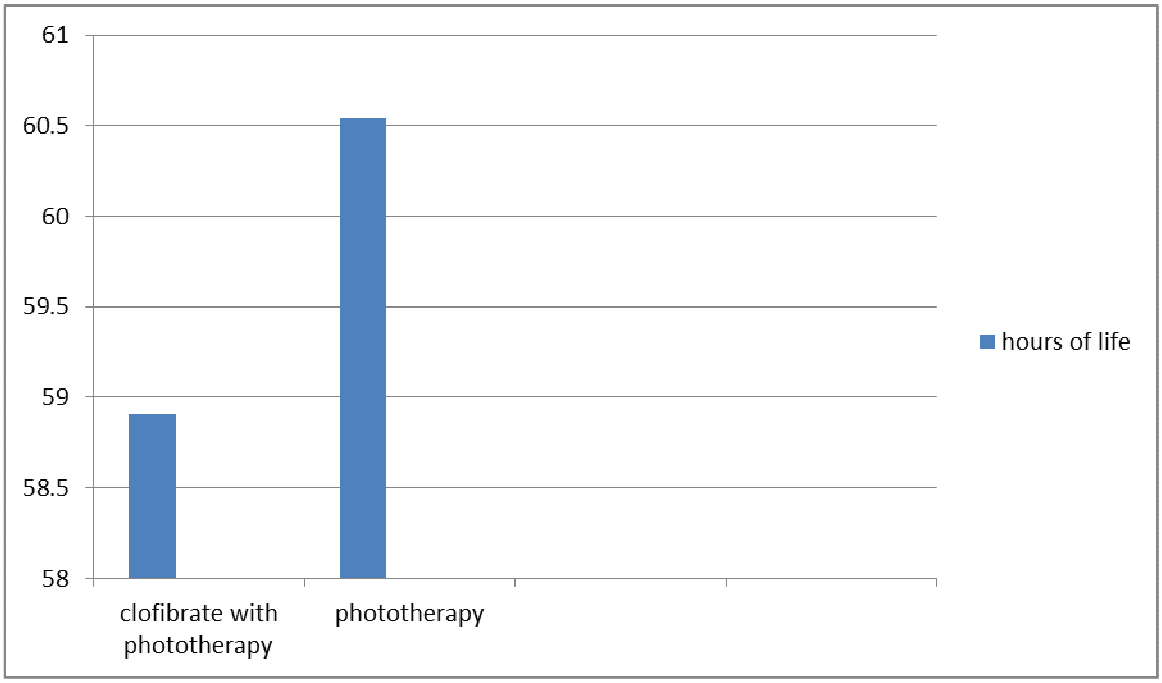


Fig3: mean age in hours at start of phototherapy in either groups

There were 99 babies in each group and they were enrolled into study when their respective serum bilirubin crossed age specific threshold for phototherapy by AAP nomogram for start of phototherapy.Babies were predominantly presenting in the age group of 24-72 hours And babies those presented in the first 24 hours were those with blood Group incompatiblity. Age in hours at the start of phototherapy is depicted in table below for babies of either group.

Hours of life	Clofibrate with phototherapy	phototherapy	Total
< 24 hrs	1(1.01%)	1(1.01%)	2(1.01%)
24- 72 hrs	81(81.81%)	85(85.85%)	166(83.83%)
72-120 hrs	17(17.17%)	13(13.13%)	30(15.15%)

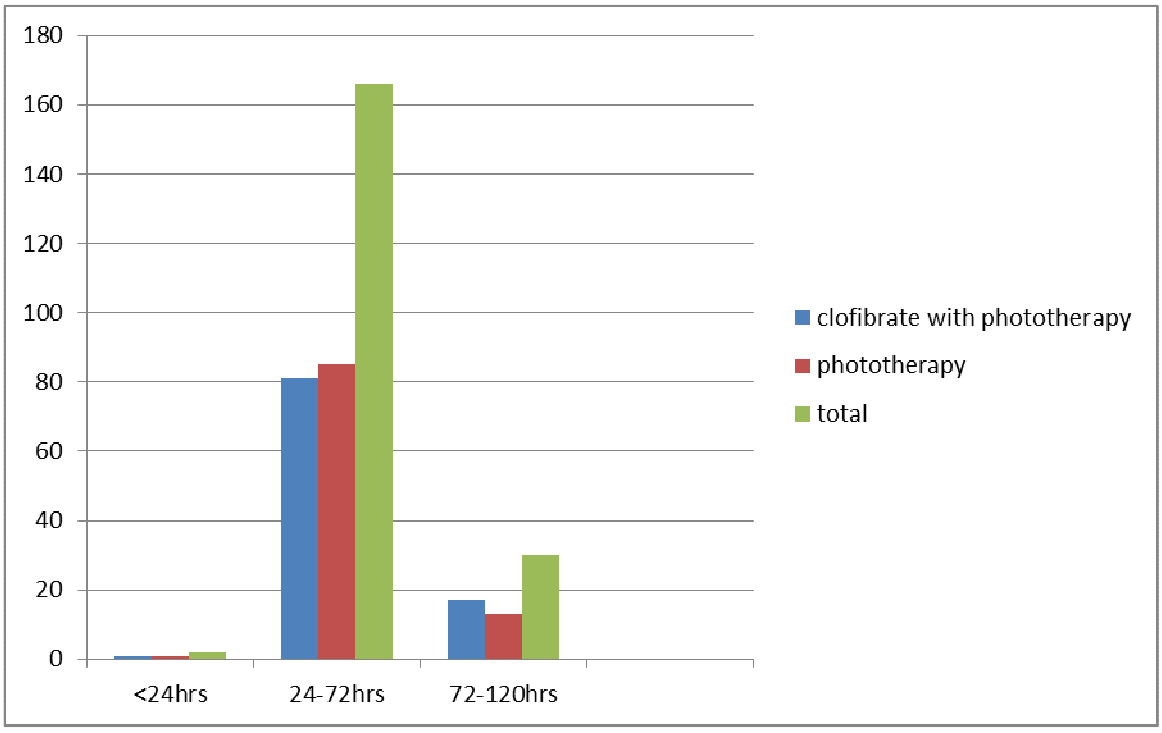


Fig4**: age distribution ranges in either groups at start of phototherapy**

CHI QUARE TEST

	value	Degree of freedom	P value
Pearson chi square test	0.192	2	p>0.05
No. of valid case	198		

There is no significant difference in number of patient started phototherapy according to hours of life at start of phototherapy.

Number of patient with blood group incompatibility in both groups is presented in following table. Though babies were not evaluated for minor blood group incompatibility ABO incompatibility was the common form of incompatibility.

Group	Rh incompatiblity	ABO incompatiblity	Total
Clofibrate with phototherapy	3(3.03%)	22(22.22%)	25(25.25%)
phototherapy	1(1.01%)	14(14.14%)	15(15.15%)

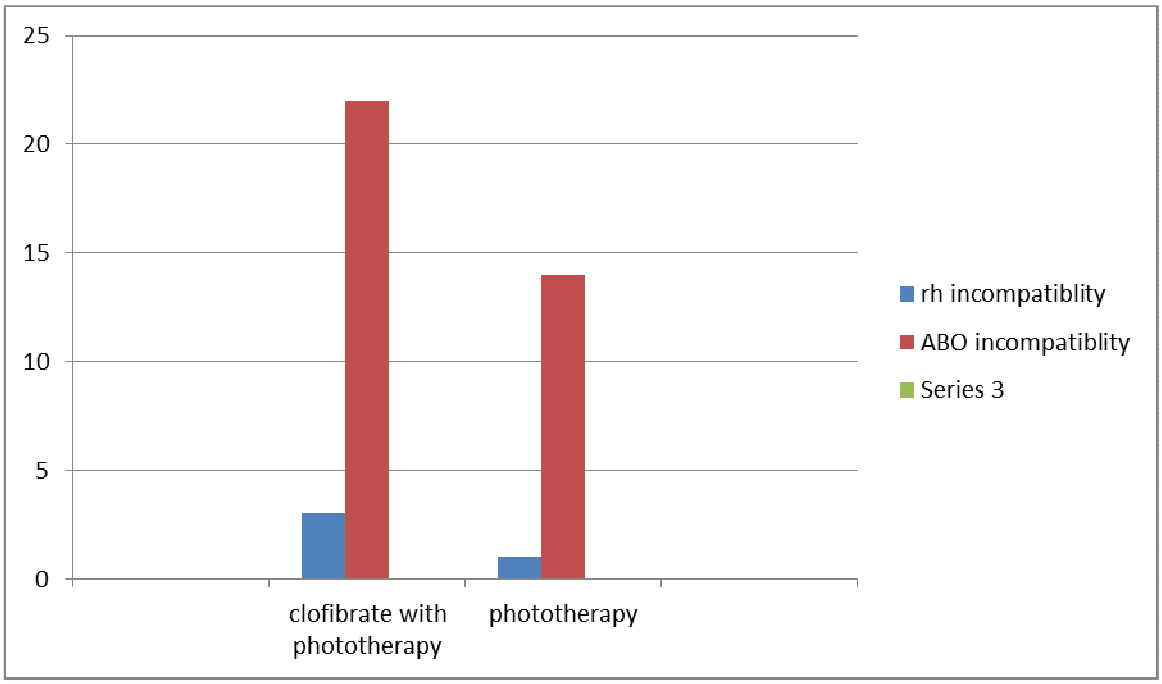


Fig **5: blood group incompatibility in either group**

CHI SQUARE TEST

	value	**Degree of freedom**	**P value**
Pearson chi square test	1.84	1	p>0.05
No . of valid cases	198		

Though there was increased number of patients in clofibrate group with blood group incompatibility there was no statistical significance in number of patient with blood group incompatibility in either groups.

DURATION OF PHOTOTHERAPY

The mean duration of phototherapy in clofibrate groupwas 40.73 hours and it was 50.85 hours and this data is depicted in the table below .

Group	Duration of phototherapy in hours(+/-SD)
Clofibrate with phototherapy	40.73(+/-8.1)
phototherapy	50.85(+/-7.3)

These results were analysed using Z test. The Z score obtained was- 9.12 in single tailed Z test and p value <0.001 was statistically significant. There was statistically significant reduction in duration of phototherapy in clofibrate group than the phototherapy group.

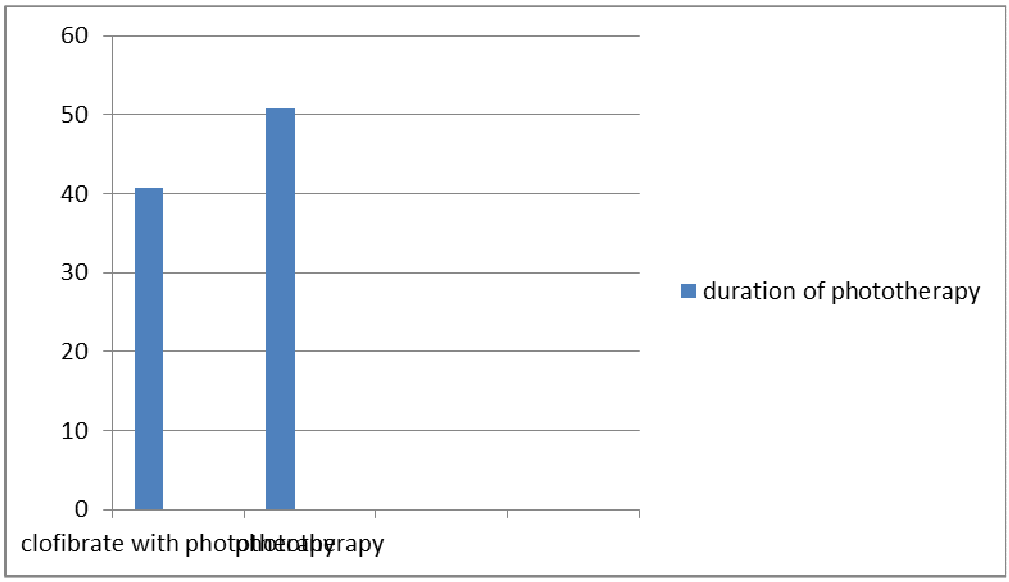


Fig **6: duration of phototherapy in either groups**

In clofibrate with phototherapy group data regarding number of patients needing different duration of phototherapy is depicted in table below

CLOFIBRATE WITH PHOTOTHERAPY GROUP

Duration of phototherapy	**No. of babies**
< 24 hours	10(10.11%)
24-48 hours	71(71.72%)
48- 96 hours	18(18.19%)

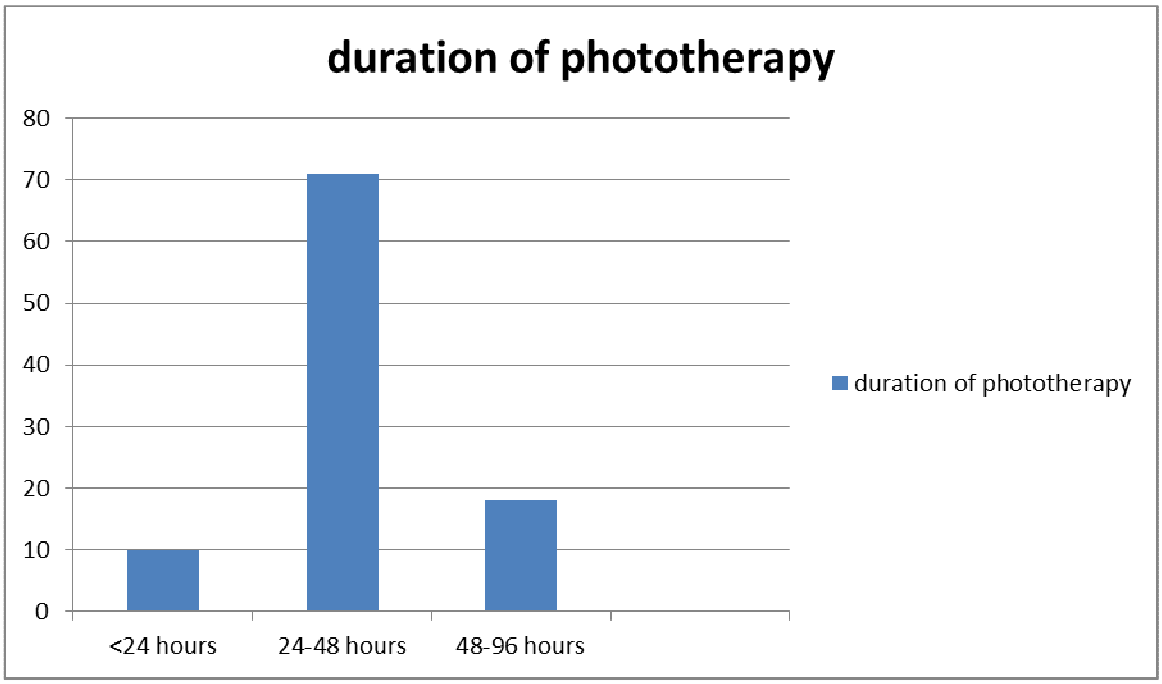


Fig 7 : duration of phototherapy in clofibrate with phototherapy

In phototherapy alone group number of patient needing different duration of phototherapy is depicted below.

Patients in phototherapy group

Duration of phototherapy	No. of babies
24-48 hours	55(55.56%)
48-96 hours	43(43.44%)
96 -120 hours	1(1.01%)

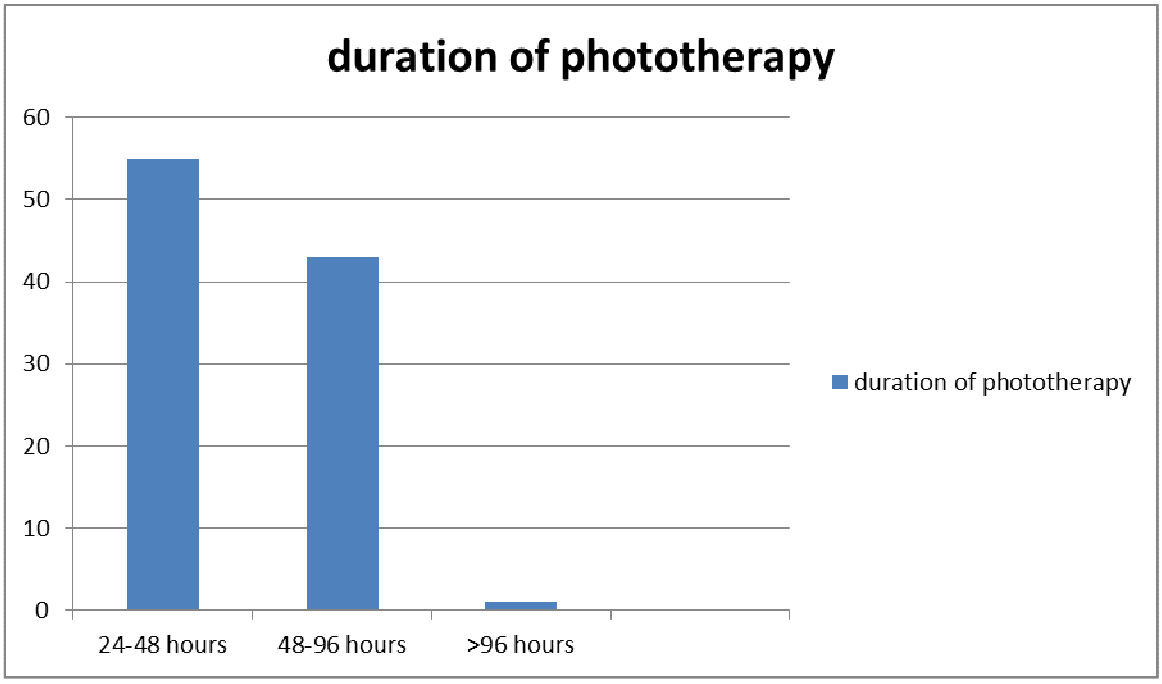


Fig 8: duration of phototherapy in phototherapy group

There was no patient who needed phototherapy for less than 24 hours and 1patient needed phototherapy for 120 hours with exchange transfusion in the phototherapy group.

Data regarding duration of phototherapy in both clofibrate with phototherapy and phototherapy were analysed . There was significant decrease in duration of phototherapy and there was significantly increased number of patient needing phototherapy for less than 48 hours in clofibrate with phototherapy group. The data is presented in following table

Duration of phototherapy	Clofibrate with phototherapy	phototherapy
< 24hours	10	0
24-48 hours	71	55
48-96 hours	18	43
>96 hours	0	1

Pearson chi square test	15.274	Degree of freedom	3	P<0.01
No. of valid cases	198			Statistically significant

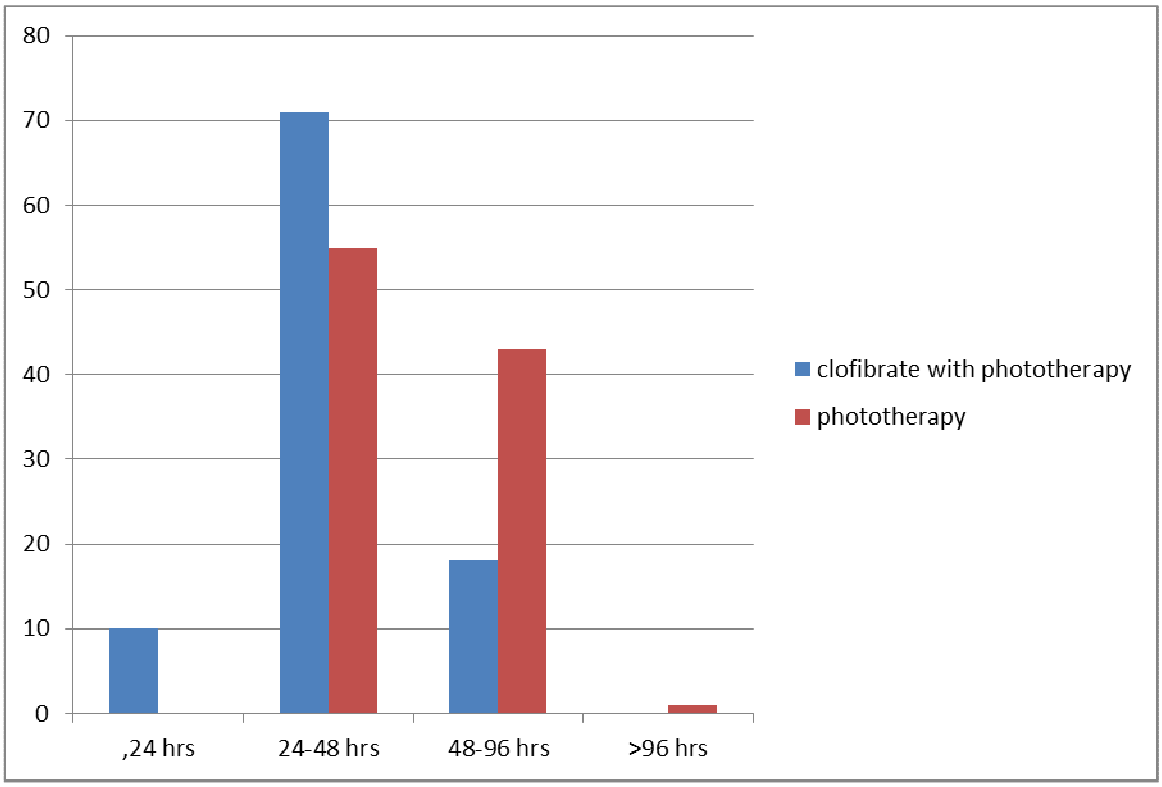


Fig 9**:duration of phototherapy in either group**

There was statistically significant decrease in duration of phototherapy in clofibrate group with predominant of patient needing phototherapy less than 48 hours.

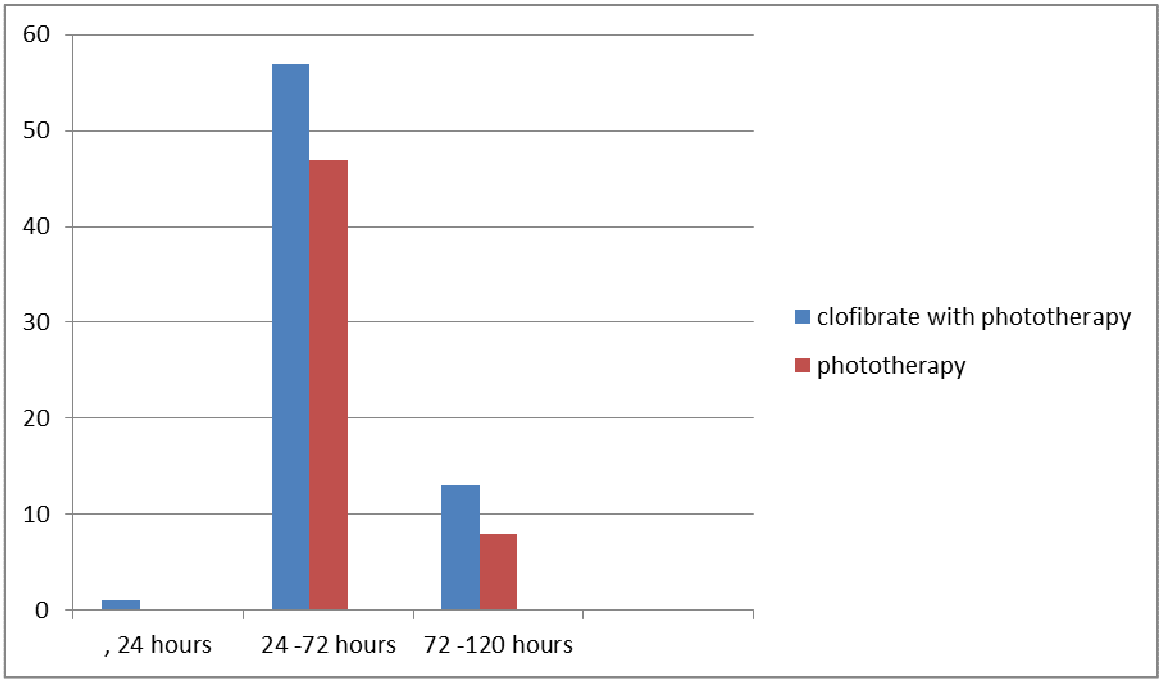
RELATION OF DURATION OF PHOTOTHERAPY TO HOURS OF LIFE AT INITIATION OF PHOTOTHERAPY

In patient needing phototherapy for 24 to 48 hours in relation to hours of life at start of phototherapy were analysed and was not statistically significant(pvalue > 0.05).

Patients needing phototherapy for 24-48 hours

Hours of life at start of phototherapy	Clofibrate with phototherapy	Phototherapy
< 24 hours	1(100%)	Ni1
24-72 hours	57(70.3%)	47(55.29%)
72 -120 hours	13(76.4%)	8(61.5%)

Fig10: duration of phototherapy- 24to 48 hours at various hours of life



DURATION OF PHOTOTHERAPY – 24 TO 48 HOURS

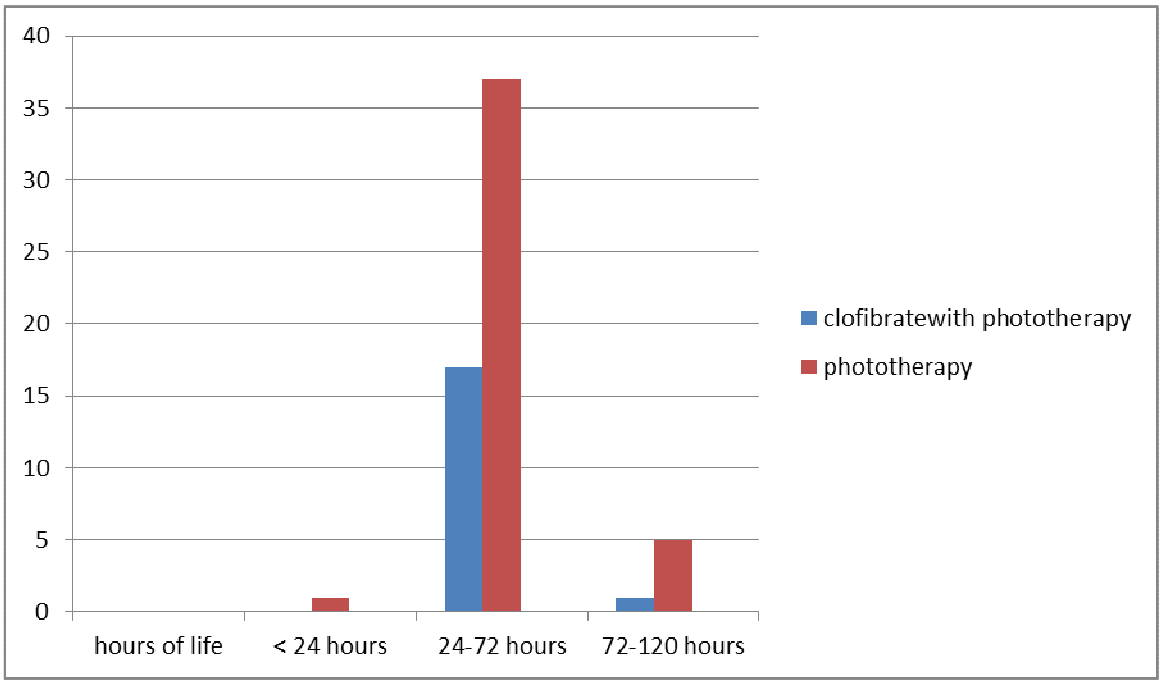
Pearson chi square test	**1.268**	**Degree of freedom**	**2**	**P value >0.05**
No.of valid cases	126			

In patients needing 48 to 96 hours of phototherapy when analysed with regards to age in hours of life at start of phototherapy the following data were obtained.

Patients needing phototherapy for 48 -96 hours

Hours of life	**Clofibrate with phototherapy**	**Phototherapy**
<24 hours	nil	1(100%)
24-72 hours	17(20.98%)	37(43.52%)
72 -120hours	1(5.8%)	5(38.46%)

Fig11:duration of phototherapy 48-96 hours at various hours of life



CHI SQUARE TEST

		Degree of freedom	P value	Result
Pearson chi square test	o.755	2	P> 0.05	Statistically insignificant
No.of valid cases	61			

PEAK BILIRUBIN

Peak bilirubin value of both the group were analysed in both the groups. In all cases except one case which went to be treated with exchange transfusion, in none of the case there was increase in serum bilirubin after start of phototherapy. Peak bilirubin corresponded to bilirubin at start of phototherapy. Data of peak bilirubin is given in the following table

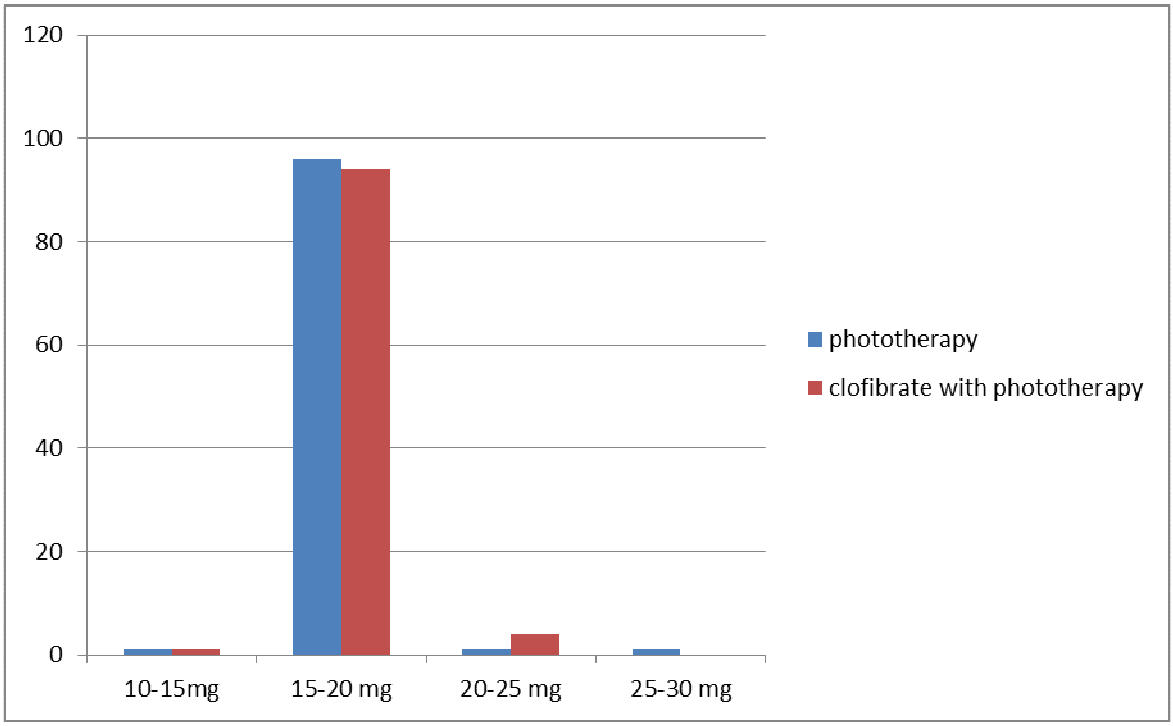
Clofibrate with phototherapy	18.63
phototherapy	18.25

This result analysed by Z test was found to be statistically not significant (p value>0.05) with Zscore of 1.01. The data on various range of peak bilirubin is presented in following table.

Peak bilirubin ranges

Bilirubin range	phototherapy	Clofibrate with phototherapy
10-15	1(1.01%)	1(1.01%)
15-20	96(96.97%)	94((94.95%)
20-25	1(1.01%)	4(4.04%)
25-30	1(1.01%)	Nil

Fig 13:peak bilirubin values



Chi square test	**2.821**	**Degree of freedom**		
No. of valid cases	198	3	p>0.05	Statistically insignificant

There was no statistically significant difference in number patient presenting their peak bilirubin between the two groups (pvalue>0.05).

RELATION OF HOURS OF LIFE AT START OF PHOTOTHERAPY WITH PEAK BILIRUBIN

The relationship of duration of life at start of phototherapy and peak bilirubin was analysed .Data is presented in the following table and data was found to be statistically insignificant(p value >0.05).

For babies with < 24 hours of life at start of phototherapy

	Peak Bilirubin 10-15	
clofibrate with phototherapy	1(100%)	Pvalue>0.05
phototherapy	1(100%)	

There was only one baby in each group who were started phototherapy at < 24 hours of life and there was no significant difference in number of patient presenting with hyperbilirubinemia in babies < 24 hours

For babies with 24 -72 hours of life at start of phototherapy

	10-15	**15-20**	**20-25**	**25-30**
Clofibrate with phototherapy	Nil	78(93.97%)	3(6.02%)	nil
phototherapy	nil	83(97.65%)	1(1.17%)	1(1.17%)

CHI SQUARE TEST

Pearson chi square test	3.57	Degree of freedom	3
No.of valid cases	166	p>0.05	Not significant

There were 81 babies in clofibrate group and 85 babies in phototherapy group and predominantly were presenting with peak bilirubin of 15 -20 mg /dl , where 96% patients of this group of babies at 24 -72 hours of life are in peak bilirubin range of 15 -20 mg/dl. On analysis p value (>0.05) was statistically insignificant.

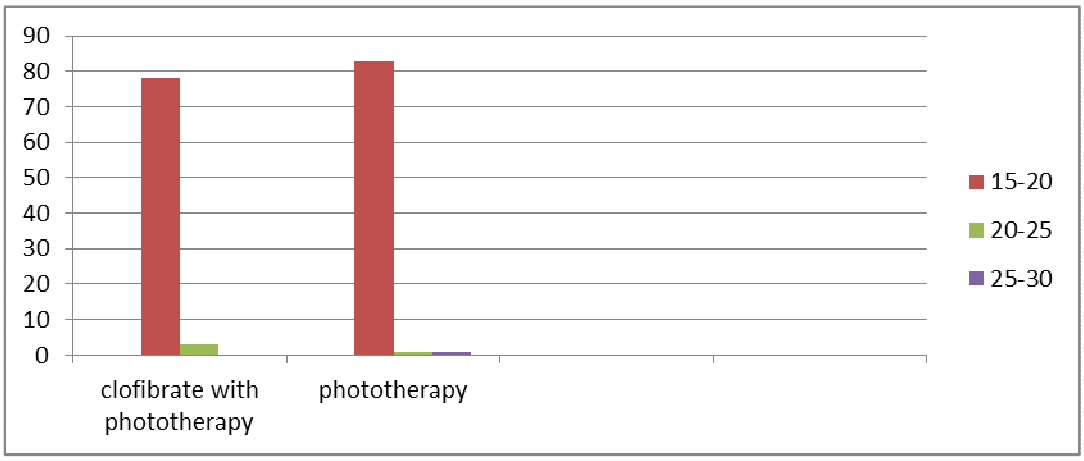


Fig **12: 24-72 hours of life at start of phototherapy and their peak bilirubin**

For babies at 72 -120 hours of life at start of phototherapy data is provided in table below.

group	**10-15**	**15-20**	**20-25**	
Clofibrate with phototherapy	Nil	16(94.11%)	1(5.89%)	Pvalue>0.05
Phototherapy	nil	13(100%)	Nil	Insignificant

CHI SQUARE TEST

Pearson chi square test	2.0690	Degree of freedom	2
No.of valid cases	30	p> 0.05	Not significant

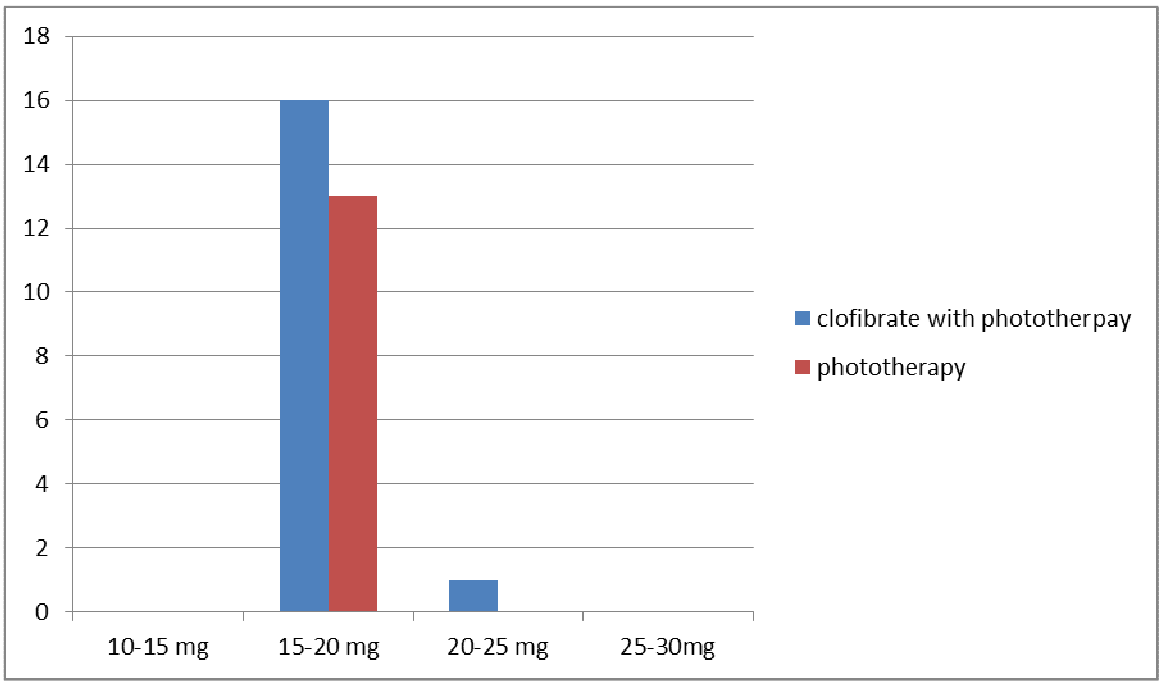


Fig 13: 72-120 hours of life at start of phototherapy and their peak bilirubin

There were 30 babies presenting in 72 -90 hours of life . Here 97 % of babies were in peak bilirubin range of 15-20 mg/dl. Of these 16 babies of clofibrate group and 13 babies of phototherapy group were in peak bilirubin range of 15-20 mg/dl.

RELATION OF PEAK BILIRUBIN WITH DURATION OF PHOTOTHERAPY

Relationship of babies peak bilirubin and duration of phototherapy was analysed and the results are in following tables Data of babies with peak bilirubin between 10 -15 mg/dl is provided in following table

Group	24 -48 hours	48 -96 hours	
Clofibrate with phototherapy	1(100%)	Nil	P value >0.05
phototherapy	Nil	1(100%)	insignificant

There were one baby in each group and there was no significant difference in either group of babies

Data for babies with peak bilirubin between 15-20 mg/dl is presented in following table.

Group	<24 hours	24-48hours	48-96 hours	Pearson chi square
Clofibrate with phototherapy	10(10.41%)	69(71.87%)	15(15.62%)	24.721
phototherapy	nil	54(57.44%)	42(44.68%)	P<0.001

CHI SQUARE TEST

PEARSON CHI SQUARE TEST	24 .721	Degree of freedom	2
No.of valid cases	190	P value <0.001	significant

Here there were 190 babies in total, of which 96 babies were in phototherapy group and 94 babies in clofibrate group. 64% of babies were needing phototherapy for 24 -48 hours in total and 71.8% of babies were in clofibrate group and 57.5 % in phototherapy group were needing phototherapy group for 24-48 hours. There was a statistically significant reduction in duration of phototherapy in patients with peakbilirubin15-20mg/dl.

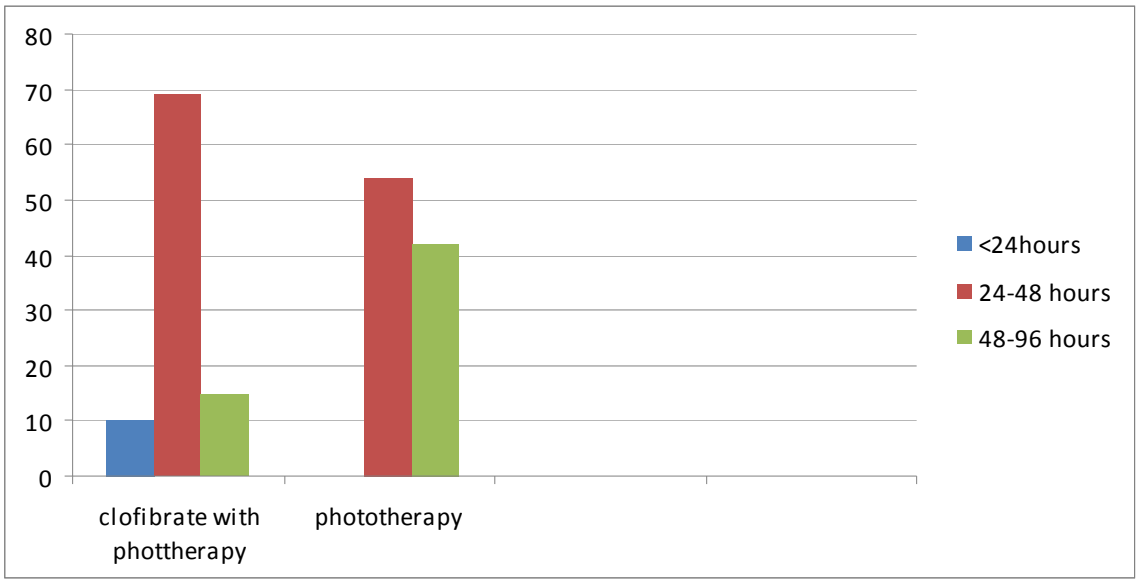


Fig **10: relation of peak bilirubin 15 -20 mg/dl and duration of phototherapy**

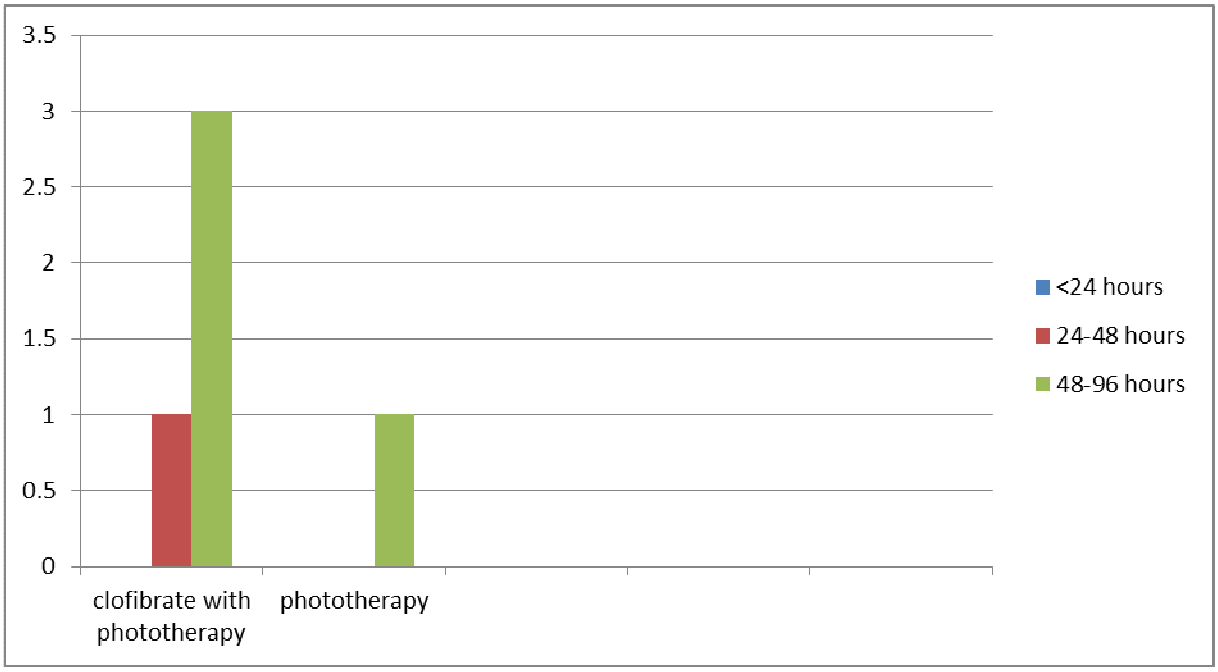
Data for babies with peak bilirubin 20-25 mg/dl is presented in following table and there were 5 babies in total of which 4 babies were in clofibrate group and 1 baby in phototherapy group. There was no significant difference in duration of phototherapy in those babies with peak bilirubin of 20 -25 mg/dl.

Group	<24hours	24-48 hours	48-96 hours	P value
Clofibrate with phototherapy	Nil	1(25%)	3(75%)	P>0.05
phototherapy	Nil	Nil	1(100%)	Insignificant

CHI SQUARE TEST

Pearson chi square test	2.8	Degree of freedom	1
No.of valid cases	5	p> 0.05	Not significant

Fig15: peak bilirubin 20-25 mg/dl and duration of phototherapy



FAILURE OF PHOTOTHERAPY/ NEED OF EXCHANGE TRANSFUSION

There was 1 case who needed exchange transfusion in phototherapy group whowas started phototherapy at 39 hours of life with peak bilirubin 25.4 and baby had ABO incompatibility needing phototherapyfor 96 hours. This baby had ABO blood group incompatibility and was coombs positive and had elevated retic count with plenty of spherocytes in smear. Baby had failure of phototherapy despite starting on double surface phototherapy This data is presented in following table There was no statistical significance in the performance of exchange transfusion.

	Exchange transfusion done	Exchange transfusion not done	Pvalue
Clofibrate with phototherapy	Nil	99(100%)	p>0.05
phototherapy	1(1.01%)	98(98.99%)	Insignificant

CHI SQUARE TEST

Pearson chi square test	2.98	Degree of freedom	1
No.of valid cases	198	p> 0.05	insignificant

Babies were followed up during hospital stay, at discharge and at 1 week following discharge and they had no complication in either group. Babies were gaining weight adequately.

DISCUSSION

Neonatal jaundice is a common clinical entity with common occurrence between 25 hours and 144 hours in 70% -80 % of term newborns and of these 20 % to 30% of newborn need phototherapy. Management of neonatal jaundice was revolutionized by use of phototherapy which has reduced the need of exchange transfusion and sequlae of bilirubin induced brain damage. Despite this effective therapy there is still difficulty in bringing down duration of phototherapy and there is still need of exchange transfusion in cases of hemolytic jaundice. This calls for need of adjunctive therapy to overcome these shortcomings in phototherapy.

Clofibrate proposed to help in these avenues was tried in this clinical entity in the later part of twentieth century . Studies earlier tried clofibrate for non hemolytic jaundice. It is now studied to be useful in cases of hemolytic jaundice.

This study had equal sex distribution and distribution of blood group incompatibility in either group. There were 55.55% of male babies in overall and this substantiates the fact male sex is a risk factor for neonatal hyperbilirubinemia[2] .In a study by Hamid et al there was 55.6% of male babies in overall enrolled in the study with 57.8% and

53.3% of babies in clofibrate and control group respectively, substantiating our observation of increased incidence of hyperbilirubinemia in male sex.

Sharafi et al in their study group had 42 % of babies were male sex and 58 % babies female sex in contrary to our observation of more male babies in our study. Sakha et al in their study had 62 % of male babies and 38 % female babies and this study was in concurrence with our observation of increased babies of male sex.

There were 40 babies in this study with blood group incompatibility accounting for 20.2 % of babies with hyperbilirubinemia . With judicious and wide coverage of Rh incompatible pregnancy with anti D globulin has reduced the occurrence of this entity. 22.2% and 14.1% of patients were with ABO incompatibility in clofibrate and phototherapy group respectively. The frequency of Rh incompatibility in Indian population is 5% and their presentation with hemolytic disease of newborn has come down with use of anti D usage. Incidence of fetomaternal ABO incompatibility is 20 -25% ,but their presentation with pathological jaundice is seen in one in ten such babies . This is because ABO antigens are weak antigens and are of carbohydrate class inducing antibodies weakly and their antigens are secretory antigen which help in

binding free antibodies, thereby reducing the load of antibody available for hemolysis.

The hours of life and the bilirubin value at onset of phototherapy was similar and statistically insignificant in either groups. There was no statistical difference in peak bilirubin value in either groups and it is found that bilirubin value did not increase further after start of phototherapy in either groups substantiating the fact phototherapy is effective mode of treatment in neonatal jaundice. Failure of phototherapy occurred only in 1 case which had ABO incompatibility but it was statistically insignificant. But this data still indicates that failure of phototherapy can still occur in phototherapy receiving babies especially in babies with blood group incompatibility.

The mean age of presentation in a study by morteza et al was 3.2 days and the bilirubin at start of phototherapy was20.6 mg/dl .The mean age at start of therapy in our study was 58.91+/-18 hrs and 60.54+/-16 hours in clofibrate and phototherapy groups respectively. The early hours of life at presentation of babies is due to early referral of extramural babies and predominance of intramural babies helping in early initiation of phototherapy There was 83% of patients in age group of 24 to 72 hours . There is no statistically significant difference in either group.

Habibi et al in their study had their patients presenting at mean age of 74 hours in phototherapy group and at 76 hours in clofibrate group, which is in concurrence with our study. Moslehi et al in their study had mean age at presentation of 126 hours in clofibrate group and 128 hours in phototherapy group. Their study had significantly delayed presentation age, which may be because of failure to include blood group incompatibility which is one of the common causes to present early with significant jaundice and failure to include these cases could explain the possibility of delayed presentation.

Moslehi et al had mean duration of phototherapy of 25 hoursin phototherapy group and 16 hours in clofibrate group and this could be because of delayed age of presentation for treatment and failure to include babies with blood group incompatibility , as these are the group that may need prolonged duration of phototherapy.

The mean duration of phototherapy is 40.73 hours and 50.85 hours in clofibrate and phototherapy group respectively . The mean duration was statistically significant with p value < 0.001. The mean time needed for phototherapy in Clofibrate group was38.8 hours and it was statistically significantly lower than control group with 68.7 hours by study done by hamid et al involving 90 children.

In clofibrate group71% of patients needed phototherapy for 24- 48 hours. There was statistically significant reduction in duration of phototherapy in different time intervals of phototherapy on comparison of two groups.

Peak bilirubin values were 18.63 and 18.25 mg/dl in clofibrate and phototherapy groups respectively. There was no statistical significance in either groups of patient. The mean bilirubin values were 18.4 mg/dl in either groups by hamida et al. Bilirubin values failed to increase with phototherapy suggesting the effectiveness of phototherapy. There was 94% and 96% of patients in clofibrate group and phototherapy group respectively with bilirubin in range 15 -20 mg/dl respectively.

Eghbalian et al in their had provided data with peak bilirubin of 20.2 mg/dl in either group which is significantly more than our study. This study does not provide data on mean age of presentation and this could not be explained.

Fallah et al had peak bilirubin of 19.4 mg/dl in clofibrate group and 19.57 mg/dl in phototherapy group which is comparable to our data. This study had included only term babies and normal birth weight babies only without any blood group incompatibility.

There was no statistical significance in relation between hours of life and peak bilirubin values in either groups.

The relation of peak bilirubin and duration of phototherapy was analysed and there was statistical significant difference in either groups in patient with peak bilirubin in 15 -20 mg/dl range with p value< 0.001. There was no statististical significance in patients with peak bilirubin in range 10 -15 mg /dl, 20-25 mg/dl.

There was failure of phototherapy in one patient with peak bilirubin in phototherapy with needing exchange transfusion and this was statistically insignificant in either groups. During follow up there was no adverse effects in either group.

In present study there was statistically significant difference in patient in duration of phototherapy and duration of phototherapy in patients with peak bilirubin values between in 15 -20 mg/dl between the two group.

CONCLUSION

Neonatal jaundice is a common entity with effective therapy in the form of phototherapy, but still the duration of phototherapy is quite prolonged affecting maternal and infant bonding. To reduce the duration of phototherapy adjunctive drugs has been tried . In this process clofibrate has come a long way and in this study it has reduced the duration of phototherapy by significant duration. There was no adverse effect during its use. Clofibrate is effective in lowering bilirubin at single low dose of 25 mg/kg at start of phototherapy. To support the use of this drug further studies on safety with long term follow up and use in sick term babies and stable preterm babies are needed.

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INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.4098/ME-1/Ethics/2012 Dt:07.06.2012.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College , Chennai reviewed and discussed the application for approval "A Study on effect of clofibrate with phototherphy vs phototheraphy in neonatal hyperbilirubinemia- a randomized controlled trial" submitted by Dr.G.R.Jaikumar, MD (Paediatrics), PG Student, KMC, Ch-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
27 JUL 2012
Kilpauk, Chennai-10.

27/7/12
CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

MASTER CHART

S. No.	Name	IPNo	Sex	Group	Hrs of Life at start of phototheraphy	mat gp	baby gp	bw	initial bilirubin	peakbil	duration of photother-aphy	Coombs	Peripheral smear	Compli-cations
1.	b/pounu	11516	M	c+pt	56hrs	o+	b+	2.6	19.4	19.4	48 hrs	coombs+	spherocytes+	nil
2.	b/nathiya	11684	M	pt	62hrs	b+	b+	3	18.2	18.2	72 hrs	-ve coombs	Ps n	nil
3.	b/rathidevi	11714	F	c+pt	51hrs	b+	ab+	3.6	17.9	17.9	36hrs	-ve coombs	psn	nil
4.	b/nirmala	11963	M	pt	60hrs	o+	a+	2.9	17.8	17.8	60 hrs	coombs +	spherocytes+	nil
5.	b/bhavani	12005	F	pt	66hrs	b+	b+	3	18.9	18.9	72hrs	-ve coombs	Ps n	ni;
6.	b/amudha	12125	M	pt	54hrs	a+	a+	2.8	17.8	17.8	36hrs	-ve coombs	Ps n	nil
7.	b/kanchana	12303	M	c+pt	58 hrs	a+	ab+	2.5	18.2	18.2	48hrs	-ve coombs	psn	nil
8.	b/radha	12083	F	c+pt	48 hrs	o+	a+	2.7	21	21	48 hrs	coombs-ve	ps n	nil
9.	b/sumathy	12170	F	c+pt	60hrs	a+	ab+	2.8	18.7	18.7	24hrs	-ve coombs	psn	nil
10.	b/zeenath	12241	F	pt	55hrs	o+	b+	2.75	18.1	18.1	48hrs	coombs-ve	ps n	nil
11.	b/shobana	12173	M	c+pt	53 hrs	b+	b+	3.2	18.8	18.8	24hrs	-ve coombs	psn	nil
12.	b/renuka	12537	M	pt	60hrs	a+	ab+	2.9	18.4	18.4	36hrs	-ve coombs	Psn	nil
13.	b/sujatha	12649	M	pt	45hrs	a+	ab+	2.6	18.1	18.1	48 hrs	-ve coombs	Ps n	nil
14.	b/mallika	12614	F	c+pt	42 hrs	o+	o+	3.1	17.7	17.7	36hrs	-ve coombs	Psn	nil
15.	b/ramya	12713	F	c+pt	56hrs	o+	a+	2.85	19.7	19.7	36hrs	coombs-ve	ps n	nil
16.	b/sharmila	12753	F	pt	66hrs	o+	o+	3.35	18.7	18.7	48hrs	-ve coombs	Ps n	nil
17.	b/vetriselvi	12795	M	pt	68hrs	a+	ab+	3.3	18.6	18.6	48hrs	-ve coombs	Ps n	nil
18.	b/deepalakshmi	12793	M	c+pt	60hrs	a+	a+	3.5	19.4	19.4	36hrs	-ve coombs	Psn	nil
19.	b/muthuselvi	12870	M	c+pt	40hrs	o+	a+	2.9	18.7	18.7	36 hrs	coombs-ve	ps n	nil
20.	b/selvi	12466	M	pt	70hrs	a+	ab+	3.2	17.6	17.6	48hrs	-ve coombs	Ps n	nil
21.	b/vetrikodi	12997	F	c+pt	64hrs	a+	a+	2.9	18.8	18.8	36hrs	-ve coombs	Psn	nil
22.	b/velvizhi	13627	F	c+pt	73hrs	b+	ab+	3.1	17.8	17.8	12hrs	-ve coombs	Ps n	nil
23.	b/valarmathi	13118	M	c+pt	67hrs	o+	a	2.9	19.3	19.3	36hrs	coombs -ve	ps n	nil
24.	b/mullaselvib/chinnammal	12764	M	pt	44hrs	b+	ab+	3.4	18.2	18.2	54 hrs	-ve coombs	Ps n	nil
25.	b/chinnammal	13058	F	pt	61hrs	ab+	b+	3.1	18.4	18.4	48hrs	-ve coombs	Ps n	nil
26.	b/sumathi	13184	F	pt	76hrs	a+	a+	3.1	18.6	18.6	48hrs	-ve coombs	Ps n	nil
27.	b/bhuvana	13274	M	pt	49hrs	a+	o+	3.2	18.8	18.8	36hrs	-ve coombs	Ps n	nil
28.	b/sumithra	13312	M	pt	70hrs	a+	a+	2.8	19.2	19.2	48hrs	-ve coombs	Ps n	nil
29.	b/vani	13287	M	c+pt	66hrs	a+	o+	2.6	18.2	18.2	48hrs	-ve coombs	Ps n	nil
30.	b/arunaiselvi	13188	F	c+pt	79hrs	b+	b+	2.8	17.8	17.8	12hrs	-ve coombs	Ps n	nil
31.	b/vasanthavalli	13234	M	c+pt	66hrs	b+	a+	3	18.3	18.3	24hrs	-ve coombs	Ps n	nil
32.	b/jeyalakshmi	13420	M	pt	60hrs	o+	o+	3	17.6	17.6	36hrs	-ve coombs	Ps n	nil

S. No.	Name	IPNo	Sex	Group	Hrs of Life at start of phototheraphy	mat gp	baby gp	bw	initial bilirubin	peakbil	duration of photother-aphy	Coombs	Peripheral smear	Compli-cations
33.	b/nirosha	13429	M	c+pt	58hrs	0-	o+	2.6	18.4	18.4	36hrs	coombs -ve	ps n	nil
34.	b/nandhini	13444	M	pt	67hrs	b+	a+	3.4	17.9	17.9	48hrs	-ve coombs	Ps n	nil
35.	b/thenmozhi	13569	M	c+pt	43hrs	b+	ab+	2.6	18.6	18.6	36hrs	-ve coombs	Ps n	nil
36.	b/valarmathi	13604	M	pt	62hrs	ab+	b+	2.5	18.1	18.1	48hrs	-ve coombs	Psn	nil
37.	b/bharani	17143	F	pt	48hrs	ab+	b+	2.7	17.5	17.5	36hrs	-ve coombs	Ps n	nil
38.	b/sangeetha	17177	F	c+pt	60hrs	a+	ab+	2.7	18.8	18.8	36hrs	-ve coombs	Ps n	nil
39.	b/suganya	17101	F	c+pt	60hrs	b-	b+	2.5	18.5	18.5	48hrs	coombs-ve	ps n	nil
40.	b/girija	17219	F	pt	48hrs	ab+	o+	3.4	16.9	16.9	36hrs	-ve coombs	Ps n	nil
41.	b/orajakumari	16898	M	c+pt	84hrs	o+	a+	2.75	19.8	19.8	36hrs	coombs +ve	spherocytes+	nil
42.	b/oshezaz	17406	M	pt	72 hrs	ab+	a+	2.8	18.5	18.5	48hrs	-ve coombs	Ps n	nil
43.	b/o revathi	18307	M	c+pt	48hrs	ab+	ab+	3.4	18.3	18.3	38hrs	-ve coombs	Ps n	nil
44.	b/osathya	18181	F	pt	60hrs	a+	o+	3	19.2	19.2	60hrs	-ve .coomb.s	Ps n	nil
45.	b/osaranya	17096	F	c+pt	72hrs	o+	a+	2.7	18.8	18.8	36hrs	coombs+ve	spherocytes+	nil
46.	b/oamul	18654	F	c+pt	60hrs	ab+	o+	2.7	19.4	19.4	30hrs	-ve coombs	Ps n	nil
47.	b/o devi	18098	F	pt	64hrs	0-	a-	3.5	17.8	17.8	48hrs	-ve coombs	Ps n	nil
48.	b/onaseema	18744	M	pt	48hrs	o+	a+	3.2	18.7	18.7	72hrs	coombs-ve	ps n	nil
49.	b/osudha	17429	M	pt	51hrs	a+	ab+	2.5	17.9	17.9	60hrs	-ve coombs	Ps n	nil
50.	b/onithya	17266	F	c+pt	60hrs	o+	a+	2.7	18.3	18.3	36hrs	coombs+ve	spherocytes+	nil
51.	b/oshanthi	17433	F	c+pt	40hrs	o+	o+	2.8	18.9	18.9	30hrs	-ve coombs	Ps n	nil
52.	b/ogeetha	17489	F	pt	60hrs	a+	0+	3.4	17.9	17.9	48hrs	-ve coombs	Ps n	nil
53.	b/oeswari	17621	F	c+pt	48hrs	o+	a+	2.6	18.3	18.3	36hrs	coombs-ve	ps n	nil
54.	b/ohemalatha	17677	M	pt	60hrs	ab+	o+	2.7	18.7	18.7	60hrs	-ve coombs	Ps n	nil
55.	b/orevathy	19629	M	c+pt	54hrs	o+	b+	3.3	17.4	17.4	24hrs	coombs-ve	ps n	nil
56.	b/ochitra	19767	M	c+pt	36hrs	a+	o+	3.4	15.4	15.4	36hrs	-ve coombs	Ps n	nil
57.	b/othavapriya	20273	F	pt	30hrs	o+	a+	2.5	18.7	18.7	60hrs	coomns+ve	spherocytes+	nil
58.	b/otharaichitra	21092	F	c+pt	108hrs	o+	a+	2.7	19.7	19.7	30hrs	coombs-ve	ps n	nil
59.	b/osathya	20317	F	pt	90hrs	o+	b+	2.5	18.9	18.9	30hrs	coombs-ve	ps n	nil
60.	b/o devi	21017	M	pt	70hrs	o-	b+	2.8	18.9	18.9	48hrs	coombs-ve	ps n	nil
61.	b/olavaya	20216	M	c+pt	60hrs	o+	o+	4.1	18.8	18.8	48hrs	-ve coombs	Ps n	nil
62.	b/omanju	20232	M	c+pt	84hrs	a+	ab+	3.3	19.2	19.2	48hrs	-ve coombs	Ps n	nil
63.	b/oporkani	20832	F	pt	72hrs	b+	o+	3.7	19.1	19.1	60hrs	-ve coombs	psn	nil
64.	b/otamilarasi	21129	F	c+pt	72hrs	o+	a+	2.8	18.4	18.4	48hrs	coombs+ve	ps n	nil
65.	b/olakshmi	20931	M	pt	70hrs	o+	a+	2.6	18.3	18.3	60hrs	coombs-ve	ps n	nil
66.	b/odharanichitra	20273	F	pt	54hrs	o+	a+	2.7	18.2	18.2	60hrs	coombs-ve	ps n	nil

S. No.	Name	IPNo	Sex	Group	Hrs of Life at start of phototheraphy	mat gp	baby gp	bw	initial bilirubin	peakbil	duration of photother-aphy	Coombs	Peripheral smear	Compli-cations
67.	b/o poongothai	21113	M	pt	56hrs	ab+	a+	2.8	18.8	18.8	42h	-ve coombs	Ps n	nil
68.	b/odhavapriya	21092	M	c+pt	48hrs	o+	o+	2.8	17.9	17.9	48hrs	-ve coombs	Ps n	nil
69.	b/omenaka	21252	F	c+pt	50hrs	o+	o+	2.5	18.8	18.8	36hrs	-ve coombs	Ps n	nil
70.	b/odhanalakshmi	29730	F	c+pt	60hrs	o+	o+	2.9	18.6	18.7	36hrs	-ve coombs	Ps n	nil
71.	b/oanandhi	21823	M	pt	70hrs	o+	o+	3.2	17.9	17.9	48hrs	-ve .coombs	Ps n	nil
72.	b/oradhidevi	21513	M	c+pt	62hrs	o+	a+	3.2	18.5	18.5	36hrs	coombs-ve	ps n	nil
73.	b/osangeetha	21850	F	pt	66hrs	o+	o+	2.5	17.9	17.9	48hrs	-ve coombs	Ps n	nil
74.	b/gomathi	22039	F	c+pt	84hrs	ab+	o+	2.9	18.2	18.2	36hrs	-ve coombs	Ps n	nil
75.	b/odhanalakshmi	22179	F	c+pt	72hrs	a+	a+	2.85	18.3	18.3	48hrs	-ve coombs	Ps n	nil
76.	b/ovani	22470	M	pt	60hrs	ab+	a+	2.5	18.9	18.9	48hrs	-ve coombs	Ps n	nil
77.	b/osafrin	22670	M	pt	72hrs	b+	o+	3	17.8	17.8	36hrs	-ve coombs	Ps n	nil
78.	b/obhuvana	22847	M	c+pt	60hrs	o+	a+	3	17.9	17.9	48hrs	-v e coombs	Ps n	nil
79.	b/osasikala	23274	M	pt	48hrs	a+	ab+	3.2	18.5	18.5	48hrs	coombs-ve	ps n	nil
80.	b/omaheshwari	23222	F	c+pt	48hrs	a+	a+	3.1	17.9	17.9	36hrs	-ve coombs	Ps n	nil
81.	b/osudha	22365	M	pt	49hrs	a+	ab+	3.4	18.9	18.9	54h	-ve coombs	Ps n	nil
82.	b/ojeyanthi	22600	F	pt	84hrs	ab+	b+	2.7	17.8	17.8	36hrs	-ve coombs	Ps n	nil
83.	b/o amala	23081	F	pt	84 hrs	a+	a+	3.1	19.2	19.2	48hrs	-ve coombs	Ps n	Nil
84.	b/o geetha	23826	M	pt	80 hrs	b+	o+	2.75	19	19	48hrs	-ve coombs	Ps n	Nil
85.	b/omariammal	24152	M	pt	66hrs	b+	b+	2.5	17.9	17.9	36hrs	-ve coombs	Ps n	Nil
86.	b/ousha	24324	M	c+pt	70hrs	o+	b+	2.9	18.8	18.8	36hrs	coombs-ve	ps n	Nil
87.	b/ovelammal	24276	F	pt	72hrs	b+	ab+	3.5	17.9	17.9	36hrs	-ve coombs	Ps n	Nil
88.	b/osaraswathy	24288	F	pt	69hrs	o+	a+	3.6	18.2	18.2	48hrs	coombs +	spherocytes+	Nil
89.	b/o nirosha	24326	M	pt	80hrs	ab+	a+	2.9	18.2	18.2	36hrs	-ve coombs	Ps n	Nil
90.	b/oazhagurani	24412	M	c+pt	84hrs	o+	o+	3.4	18.7	18.7	36hrs	-ve coombs	Ps n	Nil
91.	b/o vanaroja	24480	M	c+pt	80hrs	o+	a+	3	19.2	19.2	48hrs	coombs -	ps n	Nil
92.	b/orizwana	24375	F	c+pt	76hrs	b+	o+	3.2	18.9	18.9	36hrs	-ve coombs	Ps n	Nil
93.	b/o sumathi	25607	M	pt	79hrs	ab+	a+	2.75	17.9	17.9	36hrs	-ve coombs	Ps n	nil
94.	b/osivakami	25405	M	c+pt	68hrs	o-	o+	2.6	18.5	18.5	48hrs	coombs-	ps n	Nil
95.	b/okalaivani	25709	M	c+pt	75hrs	a+	a+	3	18.8	18.8	36hrs	Coombs –ve		Nil
96.	b/ousha	25137	F	pt	70hrs	a+	o+	3.2	18.2	18.2	48hrs	-ve .,coombs	Ps n	Nil
97.	b/okalapana	26103	M	pt	66hrs	a+	o+	2.9	18	18	48hrs	-.ve coombs	Ps n	Nil
98.	b/osaraswathy	26225	M	pt	71hrs	o+	b+	2.5	18.5	18.5	60hrs	coombs+	spherocytes+	Nil
99.	b/osrilekha	25828	F	c+pt	63hrs	a+	ab+	3.25	18.9	18.9	48hrs	-ve coombs	Ps n	Nil
100.	b/orosy	26352	M	c+pt	68hrs	a+	o+	3.5	17.7	17.7	24hrs	-ve coombs	Ps n	Nil

S. No.	Name	IPNo	Sex	Group	Hrs of Life at start of phototheraphy	mat gp	baby gp	bw	initial bilirubin	peakbil	duration of photother-aphy	Coombs	Peripheral smear	Compli-cations
101.	b/omary	26049	M	c+pt	69hrs	ab+	a+	2.75	17.5	17.5	24hrs	-ve coombs	Ps n	Nil
102.	b/ochitra	26291	M	pt	70hrs	o+	o+	2.6	18.1	18.1	48hrs	-ve coombs	Ps n	Nil
103.	b/oanbarasi	24413	F	c+pt	68hrs	b+	b+	2.5	18.5	18.5	36hrs	-ve coombs	P sn	Nil
104.	b/oaruna	25523	M	pt	70hrs	ab+	a+	2.7	17.9	17.9	48hrs	-ve coombs	Ps n	Nil
105.	b/obhuvana	27223	M	pt	66hrs	ab+	b+	2.75	16.7	16.7	36hrs	-ve coombs	P s n	Nil
106.	b/oramani	27262	M	c+pt	70hrs	ab+	a+	2.5	17.7	17.7	24hrs	-ve coombs	Ps n	Nil
107.	b/oanitha	26938	F	pt	78hrs	a+	a+	2.75	18.1	18.5	60hrs	-ve coombs	Ps n	Nil
108.	b/odevi	27237	F	c+pt	78hrs	ab+	a+	3	18.5	18.5	48hrs	-ve coombs	Ps n	Nil
109.	b/ouma	27470	M	c+pt	66hrs	a+	ab+	2.75	17.9	17.9	24hrs	-ve coombs	Ps n	Nil
110.	b/o chellammal	27478	F	pt	74hrs	o-	o+	2.7	17.3	17.8	60hrs	coombs-	ps n	Nil
111.	b/oamsavathy	27504	M	c+pt	46hrs	a+	o+	2.5	18.1	18.1	48hrs	-ve coombs	Ps n	Nil
112.	b/o gunasundari	27317	F	pt	68hrs	a+	a+	3.1	18	18	54hrs	-ve coombs	Ps n	Nil
113.	b/oumamaheshwari	27239	M	pt	82hrs	a+	ab+	2.6	19.8	19.8	48hrs	-ve coombs	Ps n	Nil
114.	b/osanthanalakshmi	27511	M	c+pt	51hrs	a+	a+	2.5	18.4	18.9	48hrs	-ve coombs	Ps n	Nil
115.	b/onirmala	27347	M	c+pt	80hrs	o-	b+	3	19.2	19.2	48hrs	-ve coombs	Ps n	Nil
116.	b/ovimala	28002	M	pt	60hrs	o+	b+	3.1	18.7	18.7	48hrs	-ve coombs	Ps n	Nil
117.	b/omanimegalai	27630	M	pt	71hrs	a+	ab+	3	18.5	18.5	36hrs	-ve coombs	Ps n	Nil
118.	b/obentica sarala	27956	F	pt	49hrs	o+	a+	3.7	21.8	25.4	96hrs	coombs+ve	spherocytes + exchange done	Nil
119.	b/okalaiselvi	27807	M	c+pt	75hrs	ab+	b+	2.75	19.4	19.5	48hrs	-ve .coombs	Ps n	Nil
120.	b/onalini	27853	M	c+pt	65hrs	o+	o+	3	19.8	19.8	48hrs	-ve coombs	Ps n	Nil
121.	b/orevathy	27798	M	pt	70hrs	o+	o+	3	18.4	18.4	60hrs	-ve coombs	Ps n	Nil
122.	b/oshakila	28287	F	pt	66hrs	a+	ab+	3.5	18.8	18.8	60hrs	-ve coombs	Ps n	Nil
123.	b/omanjula	28491	F	c+pt	53hrs	b+	o+	2.8	19.4	19.4	36hrs	-ve coombs	Ps n	Nil
124.	b/omadhavi	28969	M	c+pt	66hrs	o+	ab+	2.5	19.1	19.1	36hrs	-ve coombs	Ps n	Nil
125.	bokalpana	29191	M	c+pt	73hrs	o+	o+	2.8	18.5	18.5	30hrs	-ve coombs	Ps n	Nil
126.	b/olakshmi	29464	M	pt	77hrs	a+	o+	3	19.3	19.3	48hrs	-ve coombs	Ps n	Nil
127.	b/o kannaki	29561	M	pt	79hrs	a+	o+	3.4	18.7	18.7	60hrs	-ve coombs	Ps n	Nil
128.	b/okamala	29576	M	c+pt	83hrs	o+	a+	3.2	19.3	19.3	48hrs	coombs-ve	ps n	Nil
129.	b/omallika	29587	F	pt	67hrs	a+	a+	3.1	18.8	18.8	48hrs	-ve coombs	Ps n	Nil
130.	b/onalina	29621	M	c+pt	56hrs	a+	o+	3.2	19.4	19.4	48hrs	-ve coombs	Ps n	Nil
131.	b/ojanani	29643	F	pt	65hrs	a+	a+	3.1	18.9	18.9	60hrs	-ve coombs	Ps n	Nil

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132.	b/osundari	29663	F	pt	48hrs	o+	o+	2.6	18.5	18.5	60hrs	-ve coombs	Ps n	Nil
133.	b/osujatha	29673	F	pt	53hrs	a+	o+	2.7	18.9	18.9	48hrs	-ve coombs	Ps n	Nil
134.	b/oanjali	29698	M	c+pt	49hrs	a+	o+	2.9	18.6	18.6	54hrs	-ve coombs	Ps n	Nil
135.	b/obarathi	29689	M	c+pt	43hrs	a+	a+	2.8	19.4	19.4	54hrs	-ve coombs	Ps n	Nil
136.	b/okumare	29732	M	pt	49hrs	o+	ab+	3.2	18.9	18.9	48hrs	-ve coombs	Ps n	Nil
137.	b/osandhya	29745	F	pt	55hrs	a+	ab+	3.5	18.9	18.9	60hrs	-ve coombs	Ps n	Nil
138.	b/osaranya	29752	M	pt	43hrs	a+	a+	3.1	19.4	19.4	72hrs	-ve coombs	Ps n	Nil
139.	b/omallika	29761	F	c+pt	42hrs	ab+	a+	2.8	18.9	18.9	60hrs	-ve coombs	Ps n	Nil
140.	b/opriya	29769	F	c+pt	48hrs	o+	b+	2.7	19.1	19.1	48hrs	-ve coombs	Ps n	Nil
141.	b/osalini	29771	M	c+pt	61hrs	b+	b+	2.5	18.9	18.9	48hrs	-ve coombs	Ps n	Nil
142.	b/oyamini	29789	M	pt	38hrs	o+	0+	2.9	18.3	18.3	60hrs	-ve coombs	Ps n	Nil
143.	b/obeula	29801	F	pt	45hrs	b+	o+	2.7	18.6	18.6	48hrs	-ve coombs	Ps n	Nil
144.	b/ovanaja	29832	M	c+pt	49hrs	o+	a+	3.2	20.1	20.1	60hrs	coombs-ve	ps n	Nil
145.	b/oshenbagam	29898	F	c+pt	54hrs	b+	o+	2.7	19.3	19.3	36hrs	-ve coombs	Ps n	Nil
146.	b/osunila	29906	M	pt	60hrs	ab+	o+	3.1	18.1	18.1	48hrs	-ve coombs	Ps n	Nil
147.	b/ovennila	29945	F	pt	64hrs	a+	o+	2.7	18.6	18.6	48hrs	-ve coombs	Ps n	Nil
148.	b/oalamelu	29998	M	c+pt	46hrs	a+	o+	3.1	18.6	18.6	36hrs	-ve coombs	Ps n	Nil
149.	b/oandal	30021	F	c+pt	48hrs	o+	a+	3.5	19.6	19.6	48hrs	coombs +ve	spherocytes+	Nil
150.	b/o nancy	30072	M	pt	39hrs	a+	o+	3.2	18.9	18.9	60hrs	-ve coombs	Ps n	Nil
151.	b/osulaima	30121	M	pt	49hrs	a+	a+	2.6	18.7	18.7	48hrs	-ve coombs	Ps n	Nil
152.	b/ovelankanni	30165	M	c+pt	59h	o+	o+	3.1	19.1	19.1	36hrs	-ve coombs	Ps n	Nil
153.	b/okumari	30198	F	c+pt	65hrs	a+	ab+	2.5	18.4	18.4	36hrs	-ve coombs	Ps n	Nil
154.	b/o shobana	30212	F	c+pt	32h	a+	a-	3.1	17.3	17.3	48hrs	-ve coombs	Ps n	Nil
155.	b/ojemila	30254	F	pt	46hrs	o+	ab+	3	18.4	18.4	56hrs	-ve coombs	Psn	Nil
156.	b/o mahalaksmi	30298	M	pt	54hrs	a+	a+	3.2	18.9	18.9	48hrs	-ve coombs	Ps n	nil
157.	b/osandhya	30312	F	c+pt	34h	a+	a+	2.8	18.2	18.2	60hrs	-ve coombs	Ps n	Nil
158.	b/ocatherine	30345	M	c+pt	47hrs	o+	ab+	3.1	19.1	19.1	48hrs	-ve coombs	Ps n	Nil
159.	b/odivya	30398	F	c+pt	65hrs	a+	ab+	2.9	18.9	18.9	36hrs	-ve coombs	Ps n	Nil
160.	b/okanaga	30421	F	c+pt	47hrs	a+	a+	2.6	17.2	17.2	24hrs	-ve coombs	Ps n	Nil
161.	b/oganga	30512	M	pt	54hrs	a+	o+	3.1	18.8	18.8	36hrs	-ve coombs	Ps n	Nil
162.	b/o gunavathi	30545	F	pt	65hrs	a+	ab+	2.9	18.1	18.1	54hrs	-ve coombs	Ps n	Nil
163.	b/okumari	30598	M	c+pt	49hrs	ab+	a+	3.6	18.2	18.2	48hrs	-ve coombs	Ps n	Nil
164.	b/oparvathi	30621	F	c+pt	56hrs	a+	ab+	2.8	18.7	18.7	36hrs	-ve .coombs	Ps n	Nil
165.	b/olaxmi	30671	F	c+pt	54hrs	b+	ab+	3.1	19.2	19.3	48hrs	-ve coombs	Ps n	Nil

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166.	b/o noorjahan	30728	M	pt	39hrs	o+	ab+	3.3	18.4	18.4	60hrs	-ve coombs	Ps n	Nil
167.	b/oilayapriya	30739	M	pt	45hrs	a+	ab+	2.6	17.9	17.9	48hrs	-ve coombs	Ps n	Nil
168.	b/ojunaina	30789	M	c+pt	38hrs	o+	a+	3.2	17.3	17.3	48hrs	-ve coombs	Ps n	Nil
169.	b/ooviya	30833	F	c+pt	48hrs	ab+	a+	3	18.8	18.8	36hrs	-ve coombs	Ps n	Nil
170.	b/oramya	30894	M	pt	56hrs	ab+	a+	3.4	18.1	18.1	54hrs	-ve coombs	Psn	Nil
171.	b/ofathima	30912	F	pt	47hrs	b+	ab+	3.1	18.9	18.9	54hrs	-ve coombs	Ps n	Nil
172.	b/opunitha	30988	F	pt	59h	a+	a+	3.4	17.9	17.9	60hrs	-ve coombs	Ps n	Nil
173.	b/orahima	31092	M	c+pt	43hrs	a+	ab+	2.6	17.6	17.6	36hrs	-ve coombs	Ps n	Nii
174.	b/o tamilselvi	31043	M	c+pt	48hrs	a+	a+	2.9	20.1	20.1	48hrs	-ve coombs	Ps n	Nil
175.	b/o gayathri	31127	F	c+pt	78hrs	a+	ab+	3.1	17.9	17.9	24hrs	-ve coombs	Ps n	Nil
176.	b/ogeetha	31189	M	c+pt	40hrs	a+	a+	2.7	18.2	18.2	36hrs	-ve coombs	Psn	Nil
177.	b/ouma	31298	M	pt	49hrs	b+	ab+	2.8	18.9	18.9	54hrs	-ve coombs	Ps n	Nil
178.	b/ovanitha	31321	M	c+pt	56hrs	a+	a+	3.4	19.4	19.4	60hrs	-ve coombs	Ps n	Nil
179.	b/okalyani	31437	F	pt	67hrs	ab+	a+	2.8	18.6	18.6	48hrs	-ve coombs	Ps n	Nil
180.	b/opavithra	31469	M	c+pt	74hrs	ab+	a+	3.2	19.3	19.3	48hrs	-ve coombs	Ps n	nil
181.	b/ochinnamma	31543	F	c+pt	49hrs	a+	a+	2.8	18.9	18.9	36hrs	-ve coombs	Ps n	Nil
182.	b/orekha	31598	F	pt	52hrs	a+	ab+	3.2	18.4	18.4	48hrs	-ve coombs	Ps n	Nil
183.	b/olavanya	31643	M	pt	73hrs	a+	a+	2.6	2.6	17.9	48hrs	-ve coombs	Ps n	Nil
184.	b/okamala	31678	F	c+pt	46hrs	ab+	b+	2.8	18.2	18.2	60hrs	-ve coombs	Ps n	Nil
185.	bokalpana	31776	F	pt	43hrs	o+	o+	3.1	17.8	17.9	48hrs	-ve coombs	Ps n	Nil
186.	b/okancana	31798	M	c+pt	49hrs	a+	o+	2.8	18.1	18.1	36hrs	-ve .coombs	Ps n	Nil
187.	b/onaveena	31854	F	c+pt	56hrs	b+	a+	3.1	18.7	18.7	48hrs	-ve coombs	Ps n	Nil
188.	b/ochellamma	31987	M	pt	39hrs	o+	ab+	2.8	18.7	18.7	60hrs	-ve coombs	Ps n	Nil
189.	b/ogomati	31954	M	pt	47hrs	a+	ab+	2.6	18.6	18.6	48hrs	-ve coombs	Ps n	nil
190.	b/osridevi	32003	M	pt	56hrs	ab+	a+	2.7	17.8	17.8	54hrs	-ve coombs	Ps n	Nil
191.	b/ojayanthi	32112	F	c+pt	47hrs	a+	ab+	2.9	18.1	18.1	36hrs	-ve coombs	psn	Nil
192.	b/okasturi	32227	F	c+pt	56hrs	a+	o+	2.7	18.9	18.9	48hrs	-ve coombs	Psn	Nil
193.	b/oambiga	32298	M	c+pt	35hrs	ab+	a+	3.2	17.9	17.9	36hrs	-ve coombs	Ps n	Nil
194.	b/o damayanthi	32343	F	pt	48hrs	a+	ab+	2.8	17.3	17.3	48hrs	-ve coombs	psn	Nil
195.	b/oarthi	32432	F	pt	65hrs	o+	ab+	3.1	18.5	18.5	48hrs	-ve coombs	Ps n	Nil
196.	b/odeenarani	32457	M	c+pt	42hrs	a+	a+	3.4	17.9	17.9	36hrs	-ve coombs	Ps n	Nil
197.	b/oindu	32547	F	c+pt	46hrs	a+	ab+	3.2	18.7	18.7	48hrs	-ve coombs	Ps n	Nil
198.	b/ogeetha	32654	M	pt	39hrs	o+	a+	3.6	19.1	19.1	60hrs	coombs-ve	ps n	Nil